ESPE NEWS

BRINGING THE LATEST IN PAEDIATRIC ENDOCRINOLOGY TO YOU

ESPE
European Society for Paediatric Endocrinology
Improving care of children with endocrine diseases by promoting knowledge and research

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ESPE 2021 Online

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ESPE 2021 Online – submit your abstracts by 10 May – see page 9

Welcome

Vaccines have brought much-needed hope in the face of the ongoing pandemic, but planning ahead still requires caution. Consequently, our 59th Annual Meeting in September will take place online, to ensure that we can come together as a community this year, and share the latest research in paediatric endocrinology (see page 9).

Thanks to our excellent speakers, we are fortunate in this issue of *ESPE News* to have insights into several of the talks you will be able to enjoy at ESPE 2021 Online.

On **page 6**, Ali Abbara and Waljit Dhillo review our understanding of kisspeptin's role in puberty, with exciting potential developments in its therapeutic and diagnostic use. Meanwhile, on **page 7**, Peter Kühnen examines the melanocortin 4 receptor (MC4R) agonist setmelanotide as a treatment option in rare obesity syndromes. He explains the capacity of MC4R agonists to activate different downstream signalling cascades ('biased signalling') and therefore elicit a range of effects. Supporting transgender/gender diverse youth remains a complex and topical area of healthcare. Stephen Rosenthal discusses the associated issues, which he will address in his forthcoming presentation (**page 8**).

You can find out more about ESPE 2021 Online at **www.eurospe.org/espe2021online**. As always, your contributions will form a central part of the meeting, so please make sure to submit your abstracts by 10 May 2021.

On **page 4**, we are extremely pleased to have contributions from colleagues in India about their lives in the time of COVID. Researchers Anuradha Khadilkar and Vandana Jain reflect on the pandemic's impact on their work with patients and other aspects of their research and daily lives.

The rest of the issue is bursting with the opportunities and support available to you from ESPE. These extend from grants and committee vacancies to the prospect of future events such as ESPE Schools and the postponed ESPE Science Symposium. Read on to learn more!

We thank all this issue's contributors for writing for us at such a busy and stressful time. We wish them, you, and all your families and friends, health and peace in the coming months.

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GRANTS

Research Fellowship

One Research Fellowship of €125 000 is available to support up to 2 years of research training in a centre of excellence, for those intending to pursue a career in paediatric endocrinology. The grant will also cover the fellow's living expenses. An additional €15 000 is available for the 2-year period, to cover the costs of consumables (travel and laboratory expenses).

Apply by **20 April 2021**

Find out more at **www.eurospe.org/grants-awards/grants/research-fellowship**

Undergraduate Achievement Award

The ESPE Undergraduate Achievement Award is open to all undergraduates, including those studying medicine or other subjects. It is awarded for scientific achievement in paediatric endocrinology. Recipients will receive free registration for ESPE 2021 Online in September 2021 and a grant of €750 to support their travel and accommodation at the next physical ESPE Meeting in Rome, Italy, in 2022. The student must submit an abstract as first author to the Annual ESPE Meeting.

Apply by **17 May 2021**

Find out more at **www.eurospe.org/grants-awards/grants/undergraduate-achievement-award**

Early Career Scientific Development Grant

Three grants of €2500 are available each year. This grant supports personal development by means of a short visit to an external laboratory/hospital/institute. During the COVID-19 pandemic, and while international travel restrictions are in place, it can be used for a research period of up to 3 months at your home institution. It may be used to finance the visit of an outside expert to your institution, to provide essential guidance, consultation or advice.

The grant is intended to help you:

- learn a new technique
- troubleshoot existing methods
- discuss new methods/techniques in a research seminar
- compile statistics on joint research projects
- test samples in the framework of a joint research project.

Apply by **31 May 2021**

Find out more at **www.eurospe.org/grants-awards/grants/early-career-scientific-development-grant**

Clinical Fellowship

Due to COVID-19, selection of the next intake for this fellowship has been postponed until later in 2021. At this point, those who have already applied for the 2020–2021 intake will be considered. Therefore, there will be no further call for applications this year.

Find out more at **www.eurospe.org/grants-awards/grants/clinical-fellowship**

OPPORTUNITIES

Translators needed!

We are seeking help from ESPE members to translate ESPE patient information booklets into Dutch, French, German and Spanish.

Find out more at **www.eurospe.org/news/item/15324/Could-you-translate-ESPE's-patient-information**

Inform guideline development

You can still inform the important research and guideline development being conducted by the ESPE Turner Syndrome Working Group by completing their surveys on female and male pubertal induction.

See **www.eurospe.org/news/item/15326/Inform-pubertal-induction-guideline-development**

Join an ESPE Committee

Opportunities are now available to join ESPE's Winter and Summer School Steering Committees, Science Committee, and Diabetes, Obesity & Metabolism School Steering Committee.

Apply by **6 May**, **7 June** and **30 June 2021**

Find details at **www.eurospe.org/about/vacancies**

RESOURCES

ESPE e-Learning

The ESPE e-Learning portal provides learning modules on almost all aspects of paediatric endocrinology and diabetes mellitus.

The **General Content** section features 78 chapters and over 120 real life problem-solving cases, concisely describing physiology, pathophysiology and practical approaches to management and treatment in English.

The **Resource Limited Countries** (RLC) section is targeted towards frontline healthcare providers in these areas, and provides 24 chapters and 24 real life problem-solving cases in five languages (English, French, Spanish, Chinese and Swahili). A recent article highlights the development of our RLC resource: see *JMIR Formative Research* 2020 **4** e18555.

New additions

Problem-solving cases have been added to the Courses section, under ESPE Maghreb School: 'An infant with dehydration' and 'Persistent convulsions in a 12-month-old girl'. The content is in English and French.

See **www.espe-elearning.org**
Registration is free of charge

EVENTS

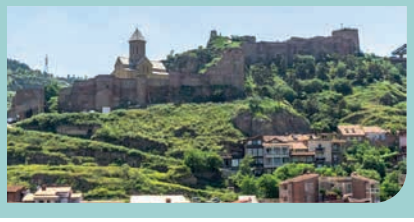
ESPE Caucasus & Central Asia School

6–9 October 2021
Tbilisi, Georgia

This school supports paediatricians who have entirely or partially completed their basic paediatric training and are either established in, or intending to develop a deep, continuing interest in, paediatric endocrinology and diabetes. The course will be held in English with slides in Russian and English in double projection.

Apply by **30 April 2021**

Find out more at **www.eurospe.org/education/caucasus-central-asia-school**



ESPE Maghreb School

23–27 November 2021
Casablanca, Morocco

This school is designed for doctors-in-training in French-speaking North African countries who have at least 3 years of experience in paediatrics, 6 months or more in endocrinology, and who hope to develop a career with a major interest in paediatric endocrinology.

Apply by **31 May 2021**

Find out more at **www.eurospe.org/education/maghreb-school**

ESPE 2021 Online

22–26 September 2021

'Lifelong endocrine care through collaboration, discovery and innovation'

Submit your abstracts now

Abstract submission by **10 May 2021**

See **www.eurospe.org/espe2021online/abstracts**

FIND OUT MORE ON **PAGE 9**

Colleagues during COVID

Following the insights from clinical colleagues in the last issue, we now take a look at the pandemic's impact on research scientists working in paediatric endocrinology in India.

Anuradha Khadilkar

Vandana Jain

"Funding has become a major issue as many grants have been diverted to combat the pandemic. In fact, sanctioned grants have been withdrawn. Sadly, we have had to reduce research staff for lack of funding"

Anuradha Khadilkar is Deputy Director and Consultant Paediatrician, with an interest in paediatric endocrinology, at Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, Pune, India.

Vandana Jain is Professor in the Department of Paediatrics at the All India Institute of Medical Sciences in New Delhi, India.

What impact has the pandemic had on your day-to-day role?

Anuradha: We undertake public health research in the community as well as working with patients. Data collection for all studies came to a grinding halt for close to 9 months. Research meetings, meeting with funding bodies and receiving medications and equipment for ongoing research were also challenging. This has affected our work. Monitoring of chronic disorders in children, treating them and reaching out to them with life-saving medication were huge struggles on a day-to-day basis.

Vandana: The pandemic has brought about a significant change in our way of working. Academics, student assessment and follow-up care have shifted to online platforms. Non-COVID patient care has been affected.

How do you feel research activities and patient care have been affected?

Anuradha: Research funding has become really difficult. Renewal of research and regulatory permissions has also become hard, as the number of people in offices is restricted. Supplementation studies that were ongoing had to be extended and end-line data collection was delayed. In our ongoing longitudinal studies, we have lost out on data for this year.

Patients have not been able to reach us because of the lockdown. They are also not coming for scheduled visits due to fear of contracting the virus. Sick children are brought in very late, putting the lives of young people, especially those with serious conditions like diabetic ketoacidosis, at risk.

Vandana: We had two ongoing randomised control trials. Enrolment came to a halt in both; the outcome assessment was missed in a few subjects and delayed in many. We tried to ensure that the subjects remained compliant by regular video calls and ensuring the supply of the intervention drug. Two new, interesting projects (which I had been trying to run for years!) were sanctioned in April/May 2020, but funds are unlikely to be released in this financial year.

Many of our follow-up patients, especially children with diabetes and congenital adrenal hyperplasia, could be reached through proactive teleconsultation. We successfully used video-conferencing platforms for our regular patient interaction programmes with children with diabetes. However, our chronic patients from disadvantaged backgrounds, illiterate patients and those from distant rural areas suffered due to poor access to technology and services. Many children with new-onset endocrine disorders (such as precocious puberty, renal tubular acidosis and adrenal tumours) were able to seek care after a delay of several months.

What has been the hardest thing to cope with?

Anuradha: Our research requires that we discuss/present our work; this has become really hard during the pandemic. Funding has become a major issue as many grants have been diverted to combat the pandemic. In fact, sanctioned grants have been withdrawn. Sadly, we have had to reduce research staff for lack of funding.

Vandana: The human touch, the easy rapport while interacting with the children and their parents in the outpatient department and wards is something I miss. With masks (and often a face shield and gown), the interaction doesn't achieve the same level of comfort. I also miss face-to-face interactive teaching of undergraduate students, at bedside and in lecture theatres.

What, if any, benefits are associated with the new ways of working?

Anuradha: While we could not work in the field or be involved in new data collection, we used the time to work on datasets which were on the 'back burner'. In some ways, discussions with our foreign collaborators have become easier, as everybody is more used to web meetings now.

Vandana: Our teleconsultation systems have developed very well. For many patients with chronic conditions, it is much more convenient and time-saving. The use of online platforms has saved me from unnecessary travel to attend administrative meetings. I have been able to finish some writing and data analysis work. It has been easy and convenient to participate in global academic programmes; the recent ESPE Connect Online 2020 meeting is a very relevant example. An international consensus guideline project that had been delayed for the last 3 years, because members were unable to meet physically at any of the common endocrine meetings, took off very nicely through videoconferencing this year.

What gives you hope?

Anuradha: Working on datasets, coming up with interesting results, publication of results in high impact journals, diagnosing rare disorders, helping children with chronic disorders and those in the community.

Vandana: The way we physicians have adapted to the situation and stood up to the challenge, from helping with management of COVID patients to continuing our non-COVID patient care, research and academic work is what gives me hope. With vaccine availability finally becoming a reality, the thought that the testing times will be behind us soon is what keeps me smiling!

Bringing you recent highlights from the world of research

Islet autoantibody dynamics in genetically predisposed children

The appearance of autoantibodies against islet proteins is useful in determining subjects at risk of type 1 diabetes (T1D).

Pöllänen and colleagues sought to understand changes in islet autoantibodies in human leukocyte antigen (HLA)-predisposed children up to the age of 15. They observed 1006 children from birth for a median of 14.9 years. The dynamics of zinc transporter 8 autoantibodies (ZnT8A), islet cell antibodies (ICA), insulin antibodies (IAA), glutamate decarboxylase antibodies (GADA) and islet antigen-2 antibodies (IA-2A) were noted, as was the presence of T1D.

Development of islet autoimmunity was seen in 275 (27.3%) at a mean age of 7.4 years, with 35 (3.5%) children diagnosed with T1D by the age of 15.5 years. ZnT8A and IAA appeared as the first autoantibodies at less than 2 years of age, whereas IA-2A and GADA increased in the preschool years, with numbers positive for GADA increasing until 10–15 years of age.

With these findings, disease subpopulations can be identified to predict and prevent T1D.

Read the full article at Pöllänen *et al.* 2020 *Journal of Clinical Endocrinology & Metabolism* **105** e4638–e4651

6-monthly s.c. leuprolide acetate for central precocious puberty

Klein *et al.* report the results of a phase 3 trial of a 6-monthly, 45mg s.c. injection of leuprolide acetate in central precocious puberty (CPP). This was approved for use by the US Food and Drug Administration in May 2020.

This open label, single arm study was performed on 64 gonadotrophin-releasing hormone agonist (GnRHa)-naive children with CPP (aged 7.5±0.1 years), who were enrolled from 25 centres across six countries. Participants received two doses (0.375ml s.c.) at 0 and 24 weeks and were followed for 48 weeks. At week 48, 49 of the 56 girls (88%) and 1 of the 2 boys achieved remission (maintained peak luteinising hormone <4IU/l at 30 minutes following GnRHa stimulation). Clinical remission could be achieved in more than 97% of participants. There were no significant adverse events to cause any discontinuation of treatment.

The authors concluded that the new preparation with a polymeric gel delivery system, administering a small volume 6-monthly, effectively suppressed pubertal hormones and stopped or caused regression of pubertal progression among children with CPP. Long term efficacy and improved quality of life and compliance with reduced frequency and reduced volume of s.c. injection need to be evaluated.

Read the full article at Klein *et al.* 2020 *Journal of Clinical Endocrinology & Metabolism* **105** e3660–e3671

Gut microbiome determines offspring's skeletal phenotype

The gut microbiome is a potential regulator of skeletal maturation both in animals and humans. Recent studies showed that, in most cases, the maternal dominant intestinal bacterial strains were transmitted to the offspring. In contrast, few studies have shown that phenotypes elicited by dominant strains are also transferred between generations.

Segmented filamentous bacteria (SFB) are intestinal bacteria that have been shown to lower bone density in healthy mice. SFB induce the expansion of intestinal osteoclastogenic Th17 cells, their migration to the bone marrow, increased secretion of interleukin-17 and the stimulation of bone resorption.

Using different germ-free and conventional mouse models, Tyagi *et al.* showed that skeletal phenotypes can be transferred by transferring the faecal microbiome, specifically SFB, through maternal contacts or cohabitation, and are independent of the mouse genetic background. Bone volume, structure and turnover of the offspring are permanently influenced.

With these results, the authors see a therapeutic option for microbiome transfer to overcome suboptimal skeletal maturation.

Read the full article at Tyagi *et al.* 2021 *eLife* **10** e64237

Sleep disturbances in children with suprasellar tumours

Sleep problems or daytime sleepiness are common in children with suprasellar tumours and are associated with reduced quality of life and increased risk of obesity. The aetiology is multifactorial, including disturbed circadian rhythm, physical damage caused by the tumour or its treatment in important hypothalamic structures that regulate sleep, and also psychological, behavioural and social environmental factors.

van Schaik and colleagues illustrate different aetiologies of disturbed sleep among four patients who benefited from specific and individualised treatment. Among these, one received nocturnal ventilation for difficulty in sleep initiation and maintenance and daytime sleepiness associated with severe obstructive sleep apnoea. Educational support was provided for another who had sleep hygiene problems causing difficulty initiating sleep, and daytime sleepiness. A patient with secondary organic hypersomnia received behavioural therapy and modafinil.

This article highlights the importance of specialised sleep investigations and provides a flowchart to aid clinicians in the diagnostics of sleep problems in children with suprasellar tumours.

Read the full article at van Schaik *et al.* 2020 *Pituitary* **23** 613–621

Starting with a kiss

Ali Abbara and Waljit Dhillo reflect on kisspeptin's potential therapeutic and diagnostic roles in hypothalamic disorders.

Ali Abbara

Waljit Dhillo

> *"Although variants causing abnormal kisspeptin signalling are exceedingly rare, their study has shed light on a fundamental constituent of the physiological control of hypothalamic GnRH secretion in humans"*

You can watch **Waljit Dhillo's** plenary talk on 22 September at ESPE 2021 Online

Understanding the enigma of kisspeptin

In 2003, two seminal reports demonstrated that inactivating variants in the kisspeptin receptor gene resulted in hypogonadotrophic hypogonadism and a failure of gonadotrophin-releasing hormone (GnRH) secretion.[1,2] An inactivating variant in the *KISS1* gene was similarly reported to result in normosmic hypogonadotrophic hypogonadism.[3] Conversely, an activating variant in the kisspeptin receptor gene led to central precocious puberty.[4] This all pointed to kisspeptin's central role in control of GnRH secretion and gonadarche.

It has since been established that hypothalamic kisspeptin neurones stimulate GnRH neurones and, in turn, the remainder of the reproductive axis. In animal models, *k*isspeptin was shown to colocalise with *n*eurokinin B and *dy*norphin in 'KNDy' neurones.[5] These neuropeptides act in an autocrine manner to generate pulsatile secretion of GnRH. Both central and peripheral administration of exogenous kisspeptin in animal models potently induces gonadotrophin secretion.[6,7]

These data place kisspeptin above GnRH at the top of the reproductive endocrine axis. Physiologically, kisspeptin neurones integrate a number of signals, such as those reflecting metabolic status, to affect hypothalamic GnRH secretion and play a key role in mediating their effects on reproductive health.

The therapeutic potential of kisspeptin

In 2005, our group was the first to administer kisspeptin to humans. We found that it potently induces gonadotrophin secretion in healthy men[8] and women.[9] From a therapeutic perspective, kisspeptin offers a unique mode of action as a hypothalamic GnRH secretagogue. With kisspeptin, stimulation of the reproductive axis remains subject to the usual feedback checks and balances, in contrast to stimulation using gonadotrophins or treatment with sex steroids.

Consequently, we looked to give kisspeptin to restore reproductive health in people with functional reproductive disorders associated with reduced hypothalamic function. For instance, functional hypothalamic amenorrhoea (FHA) is characterised by reduced pulsatile secretion of GnRH. Data from rodent models suggest that FHA is associated with reduced hypothalamic *KISS1* expression and a compensatory increase in kisspeptin receptor expression. We demonstrated that exogenous kisspeptin infusions can restore GnRH pulsatility in women with FHA.[10] Novel, stable, long-acting kisspeptin analogues offer a further avenue for realising kisspeptin's therapeutic potential to restore physiology in patients with functional hypogonadism. Recently, we reported that the kisspeptin analogue MVT-602 induces a greater gonadotrophin rise in women with FHA than in healthy women, highlighting its potential as an ovulation induction agent.[11]

Hypothalamic kisspeptin signalling is essential for the mid-cycle luteinising hormone (LH) surge and subsequent physiological ovulation.[12] Accordingly, we showed that kisspeptin-based treatments have promise in *in vitro* fertilisation treatment. A single bolus of kisspeptin induces an LH surge sufficient to efficaciously mature oocytes, but with markedly reduced rates of ovarian hyperstimulation syndrome (the major complication of using human chorionic gonadotrophin).

Kisspeptin as a diagnostic test

Kisspeptin's ability to directly stimulate the hypothalamus means it can also be used as a diagnostic test of hypothalamic function. Patients with congenital hypogonadotrophic hypogonadism (CHH) have a failure of GnRH neuronal migration or secretion. Responses to exogenous kisspeptin in CHH are markedly attenuated.[13] Furthermore, patients with anosmia (a feature more consistent with failed GnRH neuronal migration than decreased GnRH secretion) have even more diminished responses to kisspeptin than other CHH patients.[14] Likewise, patients with identified pathological variants in CHH genes have even lower LH rises in response to kisspeptin than other CHH patients.[14]

Conspicuously, up to 20% of patients with CHH can have spontaneous reversal and regain of hypothalamic GnRH function.[15] Notably, these patients regain responsiveness to kisspeptin following reversal of CHH.[15] Thus, kisspeptin could be used to test a patient's current hypothalamic function and to rapidly identify reversal of CHH.

These data suggest that kisspeptin could be useful in investigation of children with delayed puberty. Most have constitutional delay of growth and puberty (CDGP) and will spontaneously initiate puberty in time. However, some will have CHH and require treatment. Kisspeptin was evaluated as a diagnostic test in 16 children with delayed puberty, and response to kisspeptin was associated with CDGP rather than CHH.[16] Work in a larger group of patients with delayed puberty is needed to confirm kisspeptin's potential as a clinical diagnostic test.

In summary

Kisspeptin's discovery has been a major advance in understanding the hypothalamic initiation of puberty. Although variants causing abnormal kisspeptin signalling are exceedingly rare, their study has shed light on a fundamental constituent of the physiological control of hypothalamic GnRH secretion in humans. Future work will pursue research to realise kisspeptin's therapeutic and diagnostic potential in improving patient health.

Ali Abbara and Waljit S Dhillo
Section of Investigative Medicine, Imperial College London, UK

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Pharmacological treatment for rare obesity syndromes

The melanocortin 4 receptor (MC4R) agonist setmelanotide offers insights into future treatment options for rare monogenic obesity, as Peter Kühnen explains.

Peter Kühnen
©Wiebke Peitz/Charité

> *It has become evident that MC4R signalling is much more complex than previously expected. This must be taken into account when the identified MC4R genetic variants of obese patients are interpreted"*

The leptin-melanocortin signalling pathway plays a pivotal role in body weight regulation (see Figure). Gene mutations in this highly conserved pathway lead to severe hyperphagia and early onset obesity.

Setmelanotide

Until recently, a pharmacological treatment option with metreleptin has been available only for leptin-deficient patients.[1] However, in the last few years, based on the results of an investigator-initiated phase 2 study[2,3] and multicentre phase 3 studies,[4] the melanocortin 4 receptor (MC4R) agonist setmelanotide has been evaluated as a treatment option for obese patients with a mutation in one of the genes *POMC* (pro-opiomelanocortin), *PCSK1* (proprotein convertase subtilisin and kexin type 1) or *LEPR* (leptin receptor).

Within the phase 3 trial, treatment led to a reduction of 25.6% in baseline body weight in *POMC*-deficient patients and of 12.5% in baseline body weight in *LEPR*-deficient patients after approximately 1 year. This weight reduction was based on a significant reduction in hunger scores.

Skin hyperpigmentation was a treatment-related adverse event. This presumably occurred due to cross-activation of the melanocortin 1 receptor (MC1R) expressed in the skin. No treatment-related serious adverse events have been observed so far.[4] Interestingly, in contrast to first generation MC4R agonists investigated in the past, no increase in blood pressure or heart rate has yet been observed in patients treated with setmelanotide.[4]

Setmelanotide has recently been approved by the US Food and Drug Administration for patients with obesity due to *POMC*, *PCSK1* or *LEPR* deficiency.

Mechanism of action

Until recently, it has been postulated that Gs signalling, and thereby activation of intracellular cyclic AMP levels, would be the major signalling cascade for MC4R-dependent regulation of satiety.

To evaluate whether recruitment of further G proteins and signalling proteins might be relevant for ligand-induced MC4R signalling, and might explain different safety profiles, *in vitro* studies were initiated. These *in vitro* assays were performed after stimulation with different ligands (e.g. setmelanotide and further melanocyte-stimulating hormone (MSH) derivatives), to gain further knowledge of the ligand-activated MC4R signalling spectrum. It was observed that setmelanotide was approximately 100-fold more potent in activating MC4R-related Gq signalling than a first generation MC4R agonist.[3] This capacity to activate different downstream signalling cascades compared with other ligands is termed *biased signalling* and might be an important aspect in explaining the different safety profiles of different MC4R agonists tested in clinical studies (e.g. increased blood pressure).

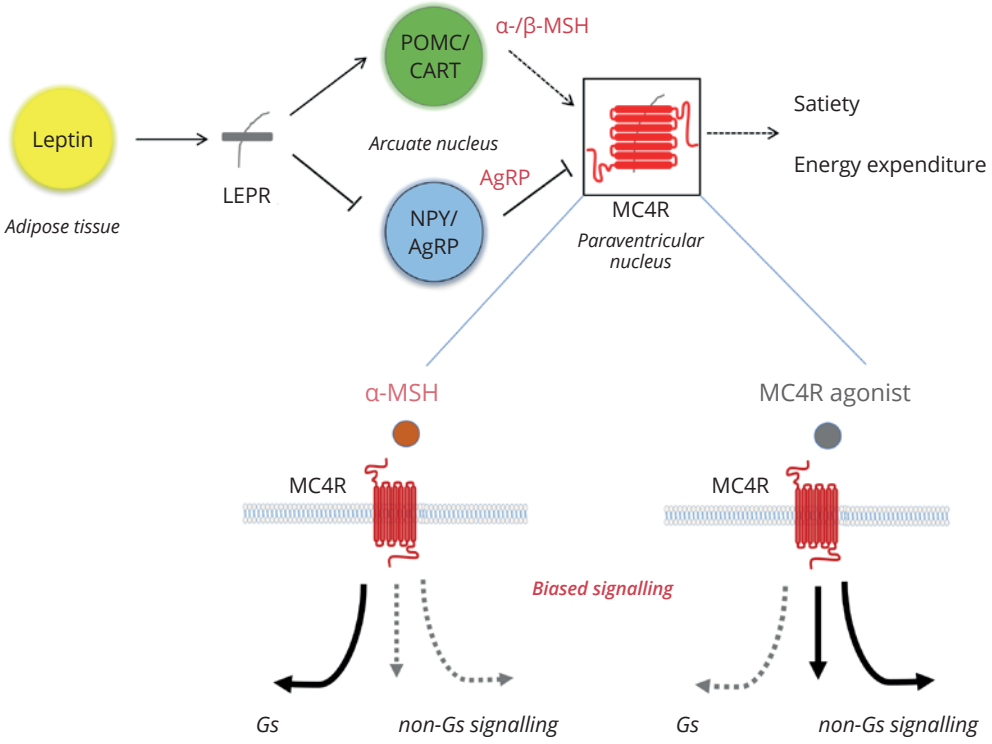

Figure. *The leptin–melanocortin pathway: leptin activates neurones expressing* POMC *by binding the LEPR. This leads to the secretion of α-/β-MSH within the arcuate nucleus. These peptides activate the G protein-coupled receptor MC4R and thereby regulate satiety and energy expenditure. Depending on the ligand, different Gs and non-Gs signalling pathways are activated (biased signalling). AgRP, agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; NPY, neuropeptide Y.*

It should be pointed out that a genetic variant in the *MC4R* gene is identified in approximately 5% of severely obese individuals. However, this genetic variant leads to impaired MC4R function in *in vitro* experiments analysing Gs signalling in only 1.7% of severely obese individuals[5] (though the identified *MC4R* genetic variants were only tested for Gs signalling).

Given the newly identified role of MC4R-related biased signalling, the significance of impaired cascades such as Gq signalling due to an *MC4R* genetic variant might be more relevant to the MSH-activated satiety signal within the hypothalamus than previously expected. Therefore, in initial studies, different *MC4R* mutations were re-evaluated regarding the recruitment of the four major G protein families, ERK activation, β-arrestin recruitment and ligand-dependent internalisation.[6] It became obvious that some *MC4R* mutations did not lead to any altered Gs signalling, but led to impaired Gq signalling and might therefore be relevant in explaining the obese phenotype of the *MC4R* variant carrier (see Figure). Based on these findings, a new *MC4R* mutation classification system has been proposed.[6,7]

Finally, it became evident that each ligand (NDP-α-MSH, α-MSH and β-MSH) tested in combination with *MC4R* genetic variants *in vitro* has its own signalling profile.[6,7]

You can watch **Peter Kühnen's** lecture on 22 September at ESPE 2021 Online

In conclusion

Setmelanotide might be a new pharmacological treatment option for patients with monogenic obesity due to mutations in the genes *POMC* or *LEPR*. Furthermore, it has become evident that MC4R signalling is much more complex than previously expected. This must be taken into account when the identified *MC4R* genetic variants of obese patients are interpreted. It is important to understand this central regulation of body weight, and to evaluate whether more common variants in one of the pathway-related genes (which might lead only to mildly impaired gene function) contribute to individual risk of developing obesity later in life. This might allow the establishment of new treatment strategies for a subgroup of patients with more common types of obesity.

Peter Kühnen
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Caring for transgender/gender diverse youth

Stephen Rosenthal considers the factors that should be taken into account when supporting transgender/gender diverse youth.

In many parts of the world, increasing numbers of transgender/gender diverse (TGD) youth are seeking medical care to bring their physical sex characteristics into alignment with their gender identity: their inner sense of self as male, female, or somewhere on the gender spectrum.

Compelling studies in the last decade have produced evidence supporting the concept that gender identity is not simply a psychosocial construct, but probably reflects a complex interplay of biological, environmental and cultural factors. In addition, while there are uncertainties in the care of TGD youth, and a need for long term safety and efficacy research, several studies have demonstrated the clear mental health benefits of gender-affirming medical care (including pubertal blockers and gender-affirming sex hormones), first pioneered by the Dutch. These have informed the Endocrine Society's current Clinical Practice Guideline for gender-dysphoric/gender-incongruent persons,[1] which was co-sponsored by ESPE and numerous other professional associations.

You can watch **Stephen Rosenthal's** plenary talk on 24 September at ESPE 2021 Online

Stephen M Rosenthal

> *"Significant barriers have recently emerged that would greatly restrict access to gender-affirming medical care"*

Despite the above-noted advances in the care of TGD youth, significant barriers have recently emerged that would greatly restrict access to gender-affirming medical care. In the UK, the High Court has issued a ruling that would prevent youths under the age of 16 from receiving pubertal blockers without a court order. In the USA, legislation pending in several states would prohibit gender-affirming medical care to those under 18 years of age and would criminalise providers who follow the existing Endocrine Society Clinical Practice Guidelines.

My upcoming presentation at the ESPE 2021 Online Meeting will review advances in our understanding of the prevalence of TGD youth, the mental health impact of gender-affirming medical care, potential adverse effects of such care, gaps in knowledge, priorities for research, and an overview of ethical dilemmas and barriers to care.

Stephen M Rosenthal
Professor of Pediatrics, University of California-San Francisco, CA, USA

Reference
1. Hembree *et al.* 2017 *Journal of Clinical Endocrinology & Metabolism* **102** 3869–3903.

ESPE 2021 Online

22–26 September 2021

'Lifelong endocrine care through collaboration, discovery and innovation'

Due to the ongoing pandemic, the 59th Annual ESPE Meeting will take place virtually on 22–26 September.

- 5 days of rich basic and clinical science
- Participate with colleagues from around the world
- Enjoy all the usual top quality sessions

A rich and diverse programme

- Plenary lectures
- Symposia
- Meet the Expert sessions
- How Do I...?
- Debates on controversies

Submit your abstracts now

The programme will feature oral communications and e-posters from scientists and clinicians around the world. Submitting an abstract to ESPE 2021 Online is an unrivalled opportunity to share your research and connect with potential collaborators.

Abstract submission deadline **10 May 2021**

See **www.eurospe.org/espe2021online/abstracts**

Make sure you're kept informed!

Register your interest at **www.eurospe.org/espe2021online**

ESPE 2022: call for programme suggestions

ESPE's 60th Annual Meeting is now scheduled for September 2022 in Rome, Italy. We are currently welcoming programme suggestions for the theme 'Personalised medicine in paediatric endocrinology'.

Submit your suggestions by **22 April 2021 (23:59 CEST)**

Send them to **espe2022@bioscientifica.com** or via **www.surveymonkey.co.uk/r/QFYLV2R**

ESPE Science Symposium: Congenital Adrenal Hyperplasia

29–30 October 2021, Nijmegen, The Netherlands

This symposium, postponed from 2020, will now take place at Radboud University Medical Centre, Nijmegen, The Netherlands, in October 2021 (unless circumstances change). It will focus on 'Congenital adrenal hyperplasia: from molecular medical research to clinical application'.

- Attendance is limited to 100, including faculty
- Delegates may come from any professional clinical and scientific discipline related directly or indirectly to the topic
- The fee is €80 per attendee, including dinner on the first night
- Accommodation is not included in this fee

ESPE offers 25 free registration spaces for young clinicians and scientists-in-training (individuals less than 8 years (full-time equivalent) since completion of doctorate training). Apply for a free place by emailing your application form (available at the web address below) to **Hedi.Claahsen@radboudumc.nl**.

Find out more and register at **www.espe-science-symposium-2021.com**

Interested in hosting next year's event?

We are seeking hosts for the 2022 Science Symposium.

Find out more at **www.eurospe.org/education/espe-science-symposium**

Apply by **30 June 2021**

Future meetings

See **www.eurospe.org/meetings** for details of all future meetings

ESPE 2021 Online
22–26 September 2021
www.eurospe.org/espe2021online

11th International Meeting of Pediatric Endocrinology
19–22 March 2022
Buenos Aires, Argentina

60th Annual ESPE Meeting
15–17 September 2022
Rome, Italy

61st Annual ESPE Meeting
September 2023
The Hague, The Netherlands

62nd Annual ESPE Meeting
September 2024
Marseille, France

OTHER EVENTS

MAY 2021

ESPE Summer School
4–7 May 2021
Online

ESPE Diabetes, Obesity & Metabolism School
9–11 May 2021
Online

OCTOBER 2021

ESPE Caucasus & Central Asia School 6–9 October 2021
Tbilisi, Georgia

ESPE Science Symposium
29–30 October 2021
Nijmegen, The Netherlands

NOVEMBER 2021

ESPE Maghreb School
23–27 November 2021
Casablanca, Morocco

All dates, deadlines and plans for 2021 are being constantly reviewed in light of COVID-19

DEADLINES

APRIL

ESPE Research Fellowship applications – 20 April 2021

ESPE Research Unit Grant final applications – 20 April 2021

ESPE 2022 programme suggestions – 22 April 2021

ESPE Caucasus & Central Asia School applications – 30 April 2021

MAY

Winter School Steering Committee applications – 6 May 2021

ESPE 2021 Online abstract submissions – 10 May 2021

ESPE Undergraduate Achievement Award applications – 17 May 2021

ESPE Early Career Scientific Development Grant applications – 31 May 2021

ESPE Maghreb School applications – 31 May 2021

JUNE

Summer School Steering Committee and Science Committee applications – 7 June 2021

ESPE Science Symposium 2022 host applications – 30 June 2021

Diabetes, Obesity & Metabolism School Steering Committee applications – 30 June 2021

ESPE
European Society for Paediatric Endocrinology

Improving care of children with endocrine diseases by promoting knowledge and research

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