Editor's Choice

Jean-Claude Carel and Ze'ev Hochberg

Forgetful adolescents

A critical role for 4 β -GABAA receptors in shaping learning deficits at puberty in mice

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Background: The onset of puberty defines a developmental stage when some learning processes are diminished, but the mechanism for this deficit remains unknown.

Results: The paper reports that, at puberty, expression of inhibitory 4 β -aminobutyric acid type A (GABAA) receptors (GABAR) increases perisynaptic to excitatory synapses in CA1 hippocampus. Shunting inhibition via these receptors reduced N-methyl-D-aspartate receptor activation, impairing induction of long-term potentiation. Pubertal mice also failed to learn a hippocampal, long-term potentiation-dependent spatial task that was easily acquired by $-/-$ mice. However, the stress steroid THP (3-OH-5 β -pregnan-20-one), which reduces tonic inhibition at puberty, facilitated learning.

Conclusions: The emergence of 4 β -GABARs at puberty impairs learning, an effect that can be reversed by a stress steroid.

Certain learning and cognitive processes decline at the onset of puberty. The pubertal process that shapes this developmental decline is unknown but is likely to involve the hippocampus, which is widely regarded as the site for learning. Shen et al. found that puberty impaired learning in mice (the time to enter a shock zone) decreased by 70%, at puberty onset. Providing the stress neurosteroid progestative allopregnanolone (THP) completely reversed the learning deficit at puberty, whereas it impaired learning before puberty via its inhibition of GABA receptors for restricting hippocampal plasticity during puberty. At puberty, but not in adults or the very young, GABA receptors were targeted perisynaptically to excitatory synapses, shunting the depolarizing current necessary for NMDA receptor activation. As a consequence, signal transmission was affected and spatial learning reduced. THP effects are distinguishable from glucocorticoids, which alters learning after a delay but has no effect acutely. Thus, the stress steroid THP provides a novel means for rapid changes in synaptic plasticity at puberty. In humans, neurosteroid depletion is consistently documented in patients with current depression and may reflect their greater chronic stress. Evidence that DHEAS is a neurosteroid, together with the fact that increases in DHEAS parallel patterns of cortical maturation from approximately age 6 years to the mid-20s, suggests that DHEAS may play an important role in extended brain maturation among humans. DHEAS has demonstrated effects on mood in humans, and acts at neuron receptor sites. I suggest three ways in which DHEAS may play a role in human brain maturation: (1) increasing activity of the amygdala; (2) increasing activity of the hippocampus, and (3) promoting synaptogenesis within the cortex.

Conversion of adult pancreatic α cells to β cells after extreme β -cell loss

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Background: Pancreatic insulin-producing β -cells have a long lifespan, such that in healthy conditions they replicate little during a lifetime. Nevertheless, they show increased self-duplication after increased metabolic demand or after injury (that is, β -cell loss). It is not known whether adult mammals can differentiate (regenerate) new β cells after extreme, total β -cell loss, as in diabetes. This would indicate differentiation from precursors or another heterologous (non- β -cell) source.

Methods: A transgenic model of diphtheria-toxin-induced acute selective near-total β -cell ablation.

Results: If given insulin, the mice survived and showed β -cell mass augmentation with time. Lineage tracing to label the glucagon-producing α cells before β -cell ablation tracked large fractions of regenerated β cells as deriving from α cells, revealing a previously disregarded degree of pancreatic cell plasticity.

Conclusion: Such inter-endocrine spontaneous adult cell conversion could be harnessed towards methods of producing β cells for diabetes therapies, either in differentiation settings in vitro or in induced regeneration.

Finding ways to restore the pancreatic β -cell mass in patients with type 1 diabetes is a challenging problem that has been addressed by several different approaches, including culture, gene transfection, fetal islet amplification, neogenesis or differentiation from stem cells. Currently, transplantation of human islets or pancreas is the only approach to replace β cells in diabetes and suffers from a lack of high-quality islets in sufficient quantity. It has been long known in animal models of diabetes due to exposure to toxic compounds such as streptozotocin that β cells could regenerate after a few months of overt diabetes. However, the exact mechanism of regeneration was not known and one limitation of these experiments was that some β cells survived to toxic exposure and could have proliferated after the initial destructive event. Here, the authors have engineered a transgenic model for virtually total ablation of pancreatic β cells, leaving intact the remaining endocrine cells. They show that over time (10 months, i.e. half a mouse lifespan) pancreatic β cells transdifferentiate from glucagon-producing α cells, after a transient step of bihormonal cells (glucagon and insulin). This results in a 44-fold increase in β -cell mass that is capable of maintaining glucose homeostasis. The interplay between α and β cells was also demonstrated earlier this year in a series of transgenic experiments where overexpression of the transcription factor Pax4 caused the conversion of α cells into β cells [1]. Depletion of α cells by this mechanism caused a neogenesis of α cells then converted to β cells resulting in a massive increase of β -cell mass. Altogether, these results indicate that there is a very significant potential for islet cell regeneration in adults that could convert into methods to restore β -cell mass in patients with diabetes [2, 3]. Conversely, the lack of such regeneration in patients further demonstrates that β -cell destruction in type 1 diabetes is not a one-time event but rather continues after diagnosis and damages new cells that might be formed by the regenerative process.

How universal are human mate choices? Size does not matter when Hadza foragers are choosing a mate

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Background: It has been argued that size matters on the human mate market: both stated preferences and mate choices have been found to be nonrandom with respect to height and weight. But how universal are these patterns? Most of the literature on human mating patterns is based on post-industrial societies. Much less is known about mating behavior in more traditional societies.

Methods: This study investigated mate choice by analyzing whether there is any evidence for nonrandom mating with respect to size and strength in a forager community, the Hadza of Tanzania. It tested whether couples assort for height, weight, body mass index (BMI), percent fat and grip strength, and whether there is a male-taller norm. Finally, it tests for an association between anthropometric variables and number of marriages.

Results: Results show no evidence for assortative mating for height, weight, BMI or percent fat; no evidence for a male-taller norm and no evidence that number of marriages is associated with our size variables. Hadza couples may assort positively for grip strength, but grip strength does not affect the number of marriages.

Conclusion: In contrast to post-industrial societies, mating appears to be random with respect to size in the Hadza.

Choosing the right mate is an important component of evolutionary fitness, particularly so in a species like our own, where long-term relationships between partners are common. There is now a large body of research investigating mating patterns within evolutionary studies of human behavior. In Western societies, size appears to matter for both mate preferences and mate choices; individuals take height into consideration when weighing up potential mates. Similarly, weight is a factor in both stated preferences. This study investigated mate choice in a hunter-gatherers society, the Hadza who live in the central Rift Valley of Tanzania. The results suggest that size and strength are not greatly important in this population mating. This lack of size-related mating patterns might appear surprising, since size is usually assumed to be an indicator of health, productivity and overall quality. But health and productivity may be signaled in alternative ways in the Hadza, who are a small, relatively homogeneous population. There may be some disadvantages to large size in a food-limited society, where the costs of maintaining large size during periods of food shortage may be high. Such disadvantages will not be seen in food-abundant societies, so that large size may be a better indicator of quality in Western populations. The authors conclude wisely that 'It is time to expand our horizon to a truly cross-cultural view and begin to sort between highly variable and truly universal mate patterns.'

Patient, physician, and consumer drivers: referrals for short stature and access to specialty drugs

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Background: Candidates for specialty drugs, the fastest growing and costliest pharmaceuticals, typically originate with primary care referrals. However, little is known about what drives such referrals – especially for large populations such as short, otherwise normal children (idiopathic short stature). Recent expanded approval of growth hormone (GH) makes more than 585,000 US children eligible for such treatment, potentially costing over USD 11 billion/year.

Methods: To quantify the relative impact of patient physiological indicators, physician characteristics, and consumer preferences on referrals to endocrinologists (and potential access to GH) for short children, a national study of 1,268 randomly selected US pediatricians was conducted, based on a full factorial experimental design in a structured survey.

Results: While patient indicators (height, growth pattern) influenced referrals ($p < 0.001$), consumer drivers (family concern) and physician attitudes had almost as great an impact – especially for children with less severe growth impairment ($p < 0.001$). Physician belief that short stature impairs emotional well-being and physician characteristics (female, older, shorter, beliefs about drug company information) increased referrals ($p < 0.03$ – 0.001) – independent of growth parameters.

Conclusions: Referral recommendations that create the pool of candidates for the specialty drug GH are heavily swayed by physician characteristics and consumer preferences, particularly in the absence of compelling physiological evidence. This makes most of children with short stature strikingly susceptible to nonphysiological influences on referrals that render them candidates for this specialty drug. Only 1 additional referral per US pediatrician would likely increase GH costs by over USD 100 million/year.

In the vast majority of cases, evaluation of a short child by a pediatric endocrinologist results from referral by a primary care physician. This paper analyzed the determinants of referrals to pediatric endocrinologists based on 4 typical case scenarios designed to vary in 5 factors – child's age and gender, child's height and growth pattern, and family concern about the child's stature. In addition, physician's attitudes towards height and short stature evaluation were surveyed. The decision to refer patients was not only based on the patients clinical characteristics (i.e. shorter patients, falling off the centile curves more likely to be referred than milder cases) but was also very much influenced by physician-dependent factors such as age, gender, height in SDS and physician's general attitude regarding short stature as a problem. Age of the child was not a factor affecting referral. In addition, family concern and the child's gender also influenced the decision to refer. These data are not fully surprising to us pediatric endocrinologists but are important for our practice and future directions. First, there is a need for higher quality evidence in our own evaluations of children with short stature [4] since better establishment of our own evaluation scheme will help in communicating it to the wider community and help referring physicians focus on patients who need a specialized evaluation most. Second, we need better evidence-based evaluation of our interventions in order to allow us to better communicate them to the medical and nonmedical community at large.

The ghosts of predators past: population cycles and the role of maternal programming under fluctuating predation risk

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Background: Maternal effects may be a major factor influencing the demography of populations. In mammals, the transmission of stress hormones between mother and offspring may play an important role in these effects. Laboratory studies have shown that stressors during pregnancy and lactation result in lifelong programming of the offspring phenotype. However, the relevance of these studies to free-living mammals is unclear. The 10-year snowshoe hare cycle is intimately linked to fluctuating predation pressure and predation risk. The enigma of these cycles is the lack of population growth following the decline phase when the predators have virtually all disappeared and the food supply is ample. A predator-induced increase in maternal stress hormone levels resulted in a decline in reproduction.

Methods: This study examines population and hormone changes over a 4-year period from the increase (2005) to the decline (2008).

Results: (1) An index of maternal stress (fecal corticosteroid metabolite [FCM] concentrations) fluctuates in synchrony with predator density during the breeding season; (2) maternal FCM levels are echoed in their offspring and this occurs at a population wide level, and (3) higher maternal FCM levels at birth are correlated with an increased responsiveness of the HPA axis in their progeny.

Conclusions: The results are the first to show an intergenerational inheritance of stress hormones in a free-ranging population of mammals. They propose that the lack of recovery of reproductive rates during the early low phase of the hare cycle may be the result of the impacts of intergenerational, maternally-inherited stress hormones caused by high predation risk during the decline phase.

Adaptations to the effects of environmental stressors are essential for ensuring individual fitness in natural populations. The environment that an individual's mother experiences affects her offspring's fitness. These nongenetic phenotypic effects can have a profound influence on offspring and can cause a resemblance not just between a mother and her offspring but also between grandparents and grand-offspring. These nongenetic maternal effects are referred to as maternal or developmental programming. A programming effect reflects the influence of a specific environmental factor during the developmental period, before or just after birth, on the organization of target tissues and/or gene-expression patterns that affect function throughout life. Mechanisms responsible for maternal programming may vary among organisms, the nature of the stressor (e.g. undernutrition, trauma, disease, psychological stress, etc.), and timing and duration of occurrence (prenatal vs. postnatal; acute vs. chronic). Glucocorticoids and their receptors play a key organization role by which these lifelong changes are brought about. This study of snowshoe hares shows that high levels of predation result in a sharp increase in levels of maternal stress hormones. These levels remain high in the offspring of these stressed animals and persist into adulthood, depressing reproduction. This suggests that the inheritance of stress levels results in a slow recovery of a population of wild mammals. The increase in stress hormones in the offspring born to stressed mothers may trade off the decrease in reproduction by increasing their offspring's antipredator behavior. Humans also inherit a stress level from their parents, and recent results suggest that this may be epigenetically determined at the glucocorticoid receptor level.

Hepatic FGF21 expression is induced at birth via PPAR α in response to milk intake and contributes to thermogenic activation of neonatal brown fat

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Background: Plasma FGF21 levels and hepatic FGF21 gene expression increase dramatically after birth in mice. This induction is initiated by suckling, requires lipid intake, is impaired in PPAR α null neonates, and is mimicked by treatment with the PPAR α activator, Wy14,643. Neonates exhibit reduced FGF21 expression in response to fasting, in contrast to the upregulation occurring in adults. Changes in FGF21 expression due to suckling or nutritional manipulations were associated with circulating free fatty acid and ketone body levels.

Results: The study mimicked the FGF21 postnatal rise by injecting FGF21 into fasting neonates, and found that this enhanced the expression of genes involved in thermogenesis within brown fat, and increased body temperature. Brown adipocytes treated with FGF21 exhibited increased expression of thermogenic genes, higher total and uncoupled respiration, and enhanced glucose oxidation.

Conclusions: The induction of FGF21 production by the liver mediates direct activation of brown fat thermogenesis during the fetal-to-neonatal transition.

Hepatic FGF21 has been discussed in our *Yearbook* in the last 2 years as a key player in metabolic adaptation to starvation, among others by stunting growth through STAT5 signaling. This year we learn that expression and plasma FGF21 levels are dramatically induced after birth, and that hepatic FGF21 induction is caused by a PPAR α -mediated effect of lipids in the milk. White fat development determines hepatic FGF21 expression in response to fasting and FGF21 released by the liver leads to activation of neonatal brown fat thermogenesis. The net effect is that mom's milk activates a pathway that turns on brown fat cells – the heat-generating cells in young animals. FGF21 expression could be quashed by preventing mice from suckling, and initiated by substituting lipids for the mother's milk. FGF21, they found, turns on genes related to activation of brown fat, and was also able to activate brown adipocytes in culture.

A new cytokine **More vasculature for more fat**

Chemerin, a novel adipokine in the regulation of angiogenesis

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Background: Chemerin is a new adipokine associated with obesity and the metabolic syndrome. Gene expression levels of chemerin were elevated in the adipose depots of obese compared with lean animals and was markedly elevated during differentiation of fibroblasts into mature adipocytes.

Objective: The objective of the study was to identify factors that affect the regulation and potential function of chemerin using a genetics approach.

Design: Plasma chemerin levels were measured in subjects from the San Antonio Family Heart Study, a large family-based genetic epidemiological study including 1,354 Mexican-American individuals.

Individuals were randomly sampled without regard to phenotype or disease status. A genome-wide association analysis using 542,944 single-nucleotide polymorphisms in a subset of 523 of the same subjects was undertaken. The effect of chemerin on angiogenesis was measured using human endothelial cells and interstitial cells in coculture in a specially formulated medium.

Results: Serum chemerin levels were found to be highly heritable ($h^2 = 0.25$; $p = 1.4 \times 10^{-9}$). The single-nucleotide polymorphism showing strongest evidence of association (rs347344; $p = 1.4 \times 10^{-6}$) was located within the gene encoding epithelial growth factor-like repeats and discoidin I-like domains 3, which has a known role in angiogenesis. Functional angiogenesis assays in human endothelial cells confirmed that chemerin significantly mediated the formation of blood vessels to a similar extent as vascular endothelial growth factor.

Conclusion: Plasma chemerin levels are significantly heritable and identified a novel role for chemerin as a stimulator of angiogenesis.

Chemerin was reported in 2007 as a new adipokine elevated in states of obesity and the metabolic syndrome. Chemerin gene expression was significantly elevated in the adipose depots of obese compared with lean animals and was predominantly expressed by adipocytes rather than stromal and vascular cells in adipose tissue. In vitro studies have shown that chemerin expression and secretion was markedly up-regulated during differentiation of fibroblasts to mature adipocytes and was approximately 20-fold higher in fully differentiated adipocytes compared with undifferentiated fibroblasts. Furthermore, recombinant chemerin was shown to stimulate 3T3-L1 adipocyte function such as glucose transport, and plasma chemerin levels were significantly associated with characteristics of the metabolic syndrome, including body mass index, plasma triglycerides, and blood pressure in several independent human populations. This article demonstrates for the first time that variation in plasma chemerin levels is significantly heritable, and a number of polymorphisms in candidate genes that may influence plasma chemerin levels are identified. Of particular interest is a gene that has been previously shown to play a role in angiogenesis. Because the expansion of adipose tissue is dependent on the formation of new blood vessels, and given the significant association already established between chemerin and obesity, this group explored the effects of chemerin on angiogenesis and found that recombinant chemerin promoted the formation of new blood vessels. These novel data indicate a new role for chemerin in the formation of new blood vessels, and this may be an essential component of adipose tissue expansion.

Concept revised **Synchronizing the mothering hormone**

Synchronized network oscillations in rat tuberoinfundibular dopamine neurons: switch to tonic discharge by thyrotropin-releasing hormone

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Background: The pituitary hormone, prolactin, triggers lactation in nursing mothers. Under nonlactating conditions, prolactin secretion is suppressed by powerful inhibition from hypothalamic tuberoinfundibular dopamine (TIDA) neurons. Although a firing pattern has been suggested as integral to neuroendocrine control, the electrical behavior of TIDA cells remains unknown.

Results: This report demonstrates that rat TIDA neurons discharge rhythmically in a robust 0.05-Hz oscillation. The oscillation is phase locked between neurons, and while it persists during chemical synaptic transmission blockade, it is abolished by gap junction antagonists. Thyrotropin-releasing hormone (TRH) potently stimulates prolactin release, an effect assumed to take place in the pituitary. In TIDA cells, TRH caused a transition from phasic to tonic firing through combined pre- and postsynaptic effects.

Conclusions: These findings suggest a model for prolactin regulation where a TIDA network switch from oscillations to sustained discharge converts dopamine from an antagonist at high concentrations to a functional agonist as dopamine output from the network decreases.

The reason that women normally do not produce prolactin is that its release is normally strongly inhibited by dopamine. This is secreted by cells known as 'TIDA' neurons in the hypothalamus in the brain. The study has shown that the TIDA cells normally display an extremely rhythmical activity, with discharges every 20 s, required to function as a strong inhibitor of prolactin release. Thus, it seems reasonable that the functional role of the TIDA oscillation is not to time prolactin surges but to ensure sufficient inhibitory concentrations of DA in the anterior pituitary. The study has also shown that TRH can interrupt the rhythmical signaling pattern of TIDA cells. Prolactin also plays a role in reproduction and fertility, one of which is reduction of sexual libido; it is released during an orgasm. It is believed that prolactin is significant for metabolism, since patients, and children even more, with elevated levels of prolactin become overweight. In terms of basic prolactin physiology, TRH-mediated stimulation of prolactin release occurs at the hypothalamic level by shifting TIDA oscillations to tonic discharge.

A new neurohormone Blessing blockers

Identification of human GnIH homologs, RFRP-1 and RFRP-3, and the cognate receptor, GPR147 in the human hypothalamic pituitary axis

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Background: The existence of a hypothalamic gonadotropin-inhibiting system has been elusive. A neuropeptide named gonadotropin-inhibitory hormone (GnIH) which directly inhibits gonadotropin synthesis and release from the pituitary was recently identified in quail hypothalamus.

Results: This report identifies GnIH homologs in the human hypothalamus and characterizes their distribution and biological activity. GnIH homologs were isolated from the human hypothalamus by immunoaffinity purification, and then identified as human RFRP-1 and RFRP-3 by mass spectrometry. Immunocytochemistry revealed GnIH-immunoreactive neuronal cell bodies in the dorsomedial region of the hypothalamus with axonal projections to GnRH neurons in the preoptic area as well as to the median eminence. RT-PCR and subsequent DNA sequencing of the PCR products identified human GnIH receptor (GPR147) mRNA expression in the hypothalamus as well as in the pituitary. In situ hybridization further identified the expression of GPR147 mRNA in luteinizing hormone-producing cells (gonadotropes). Human RFRP-3 has recently been shown to be a potent inhibitor of gonadotropin secretion in cultured sheep pituitary cells by inhibiting Ca^{++} mobilization. It also directly modulates GnRH neuron firing.

Conclusions: The identification of two forms of GnIH (RFRP-1 and RFRP-3) in the human hypothalamus which targets human GnRH neurons and gonadotropes and potentially inhibit gonadotropin in sheep models provides a new paradigm for the regulation of hypothalamic-pituitary-gonadal axis in man and a novel means for manipulating reproductive functions.

A neuropeptide inhibitor of gonadotropin secretion has been postulated for some years, described in birds, but remained elusive in humans. By testing the human homologs RFRP-1 and -3 to the GnIH peptide, this paper identified the GnIH. A G-protein-coupled receptor, GPR147, has been identified as their cognate receptor. GnIH neurons were observed in the dorsomedial region of the human hypothalamus in close proximity to GnRH neurons in the preoptic area, suggesting the regulation of GnRH neurons by GnIH. GnIH may regulate gonadotropin secretion by inhibiting GnRH neurons as well as directly acting on gonadotrope cells in the pituitary as was clearly demonstrated in isolated pituitary

cells in the sheep. GnIH has the potential of an alternative or adjunct therapeutic agent to inhibit gonadotropins and steroid hormones. Thus this endogenous inhibitor of gonadotropin secretion has therapeutic potential in the treatment of hormone-dependent diseases such as precocious puberty, and may also have potential as a novel contraceptive.

Important mechanism A needed assistant

A β -arrestin-biased agonist of the parathyroid hormone receptor (PTH1R) promotes bone formation independent of G-protein activation

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Background: About 40% of the therapeutic agents in use today exert their effects through seven-transmembrane receptors (7TMRs). When activated by ligands, these receptors trigger two pathways that independently transduce signals to the cell: one through heterotrimeric GTP-binding proteins (G proteins) and one through β -arrestins; so-called biased agonists can selectively activate these distinct pathways.

Methods: This study investigated selective activation of these pathways through the use of a biased agonist for the type 1 parathyroid hormone (PTH)-PTH-related protein receptor (PTH1R), (D-Trp12,Tyr34)-PTH(7–34) (PTH- β arr), which activates β -arrestin but not classic G-protein signaling.

Results: In mice, PTH- β arr induces anabolic bone formation, as does the nonselective agonist PTH(1–34), which activates both mechanisms. In β -arrestin2-null mice, the increase in bone mineral density evoked by PTH(1–34) is attenuated and that stimulated by PTH- β arr is ablated. The β -arrestin2-dependent pathway contributes primarily to trabecular bone formation and does not stimulate bone resorption.

Conclusions: These results show that a biased agonist selective for the β -arrestin pathway can elicit a response in vivo distinct from that elicited by nonselective agonists. Ligands with these properties may form the basis for improved 7TMR-directed pharmacologic agents with enhanced therapeutic specificity.

The physiologic actions of PTH were thought to be mediated by classic G-protein signaling. We now learn that the PTH GPCR can trigger signaling mechanisms that are independent from the classic G-protein pathways. β -Arrestins, a small family of intracellular proteins initially identified for their role as GPCR desensitizers, act as signal transducers through a distinct mechanism, scaffolding with accessory effector molecules. PTH stimulation of the PTH receptor promotes translocation of β -arrestins 1 and 2 to the plasma membrane, association of the receptor with β -arrestins, internalization of receptor- β -arrestin complexes, and activation of ERK1/2. This paper shows that a selective agonist for β -arrestin signaling in the absence of G-protein signaling promotes osteoblastic bone formation without stimulating bone resorption and may have clinical utility as an anabolic agent in the treatment of diseases characterized by insufficient rates of bone formation, such as osteoporosis.

Stomach ghrelin-secreting cells as food-entrainable circadian clocks

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Background: Increases in arousal and activity in anticipation of a meal, termed ‘food anticipatory activity’ (FAA), depend on circadian food-entrainable oscillators (FEOs), whose locations and output signals have long been sought. It is known that ghrelin is secreted in anticipation of a regularly scheduled meal-time.

Results: This report shows that ghrelin administration increases locomotor activity in nondeprived animals in the absence of food. In mice lacking ghrelin receptors, FAA is significantly reduced. Impressively, the cumulative rise of activity before food presentation closely approximates a gaussian function ($r = 0.99$) for both wild-type and ghrelin receptor knockout animals, with the latter having a smaller amplitude. For both groups, once an animal begins its daily anticipatory bout, it keeps running until the usual time of food availability, indicating that ghrelin affects response threshold. Oxyntic cells coexpress ghrelin and the circadian clock proteins PER1 and PER2. The expression of PER1, PER2, and ghrelin is rhythmic in light-dark cycles and in constant darkness with ad libitum food and after 48 h of food deprivation. In behaviorally arrhythmic-clock mutant mice, unlike control animals, there is no evidence of a premeal decrease in oxyntic cell ghrelin. Rhythmic ghrelin and PER expression are synchronized to prior feeding, and not to photic schedules.

Conclusions: This article concludes that oxyntic gland cells of the stomach contain FEOs, which produce a timed ghrelin output signal that acts widely at both brain and peripheral sites. It is likely that other FEOs also produce humoral signals that modulate FAA.

The body uses an endogenous circadian timing system, termed ‘food-entrainable oscillators’ (FEOs), to predict the availability of food. These activate food-seeking behaviors and enable the synthesis and secretion of enzymes necessary for digestion before mealtime. For regularly scheduled daily meals, the behavioral manifestation of this timing mechanism is the expression of food anticipatory activity (FAA), reflected in an increase in activity several hours before the appearance of food. The present studies explore the possibility that ghrelin-secreting cells of the stomach oxyntic glands are FEOs. The results show that stomach oxyntic cells fulfill several essential criteria of an FEO, and the findings provide an avenue for understanding the previous literature on FAA. Ghrelin stimulates both the appetitive (anticipatory locomotor behavior) and the consummatory component (food intake). Administration of ghrelin in the absence of food in a nondeprived animal increases activity/arousal and increases subsequent food intake. In the absence of ghrelin receptors, food anticipatory behavior is diminished. This suggests that ghrelin increases the drive to consume food. Both ghrelin and clock genes are expressed rhythmically within oxyntic cells. The phase of this rhythm is controlled by the time of food availability. Although mice cannot be deprived for many days, in humans, ghrelin release timed to previous mealtimes persists after 1–3 days of fasting. Discovery of the brain mechanisms modulating ghrelin effects on activity and eating will further the understanding of this system in the generation of FAA.

Inhibition of the c-Abl-TAp63 pathway protects mouse oocytes from chemotherapy-induced death

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Background: Germ cells are sensitive to genotoxins, and ovarian failure and infertility are major side effects of chemotherapy in young patients with cancer.

Results: The c-Abl-TAp63 pathway is activated by chemotherapeutic DNA-damaging drugs in model human cell lines and in mouse oocytes and plays a role in cell death. In cell lines, upon cisplatin treatment, c-Abl phosphorylates TAp63 on specific tyrosine residues. Such modifications affect p63 stability and induce a p63-dependent activation of proapoptotic promoters. Similarly, in oocytes, cisplatin rapidly promotes TAp63 accumulation and eventually cell death. Treatment with the c-Abl kinase inhibitor imatinib counteracts these cisplatin-induced effects.

Conclusion: The data support a model in which signals initiated by DNA double-strand breaks are detected by c-Abl, which, through its kinase activity, modulates the p63 transcriptional output. Moreover, they suggest a new use for imatinib, aimed at preserving oocytes of the follicle reserve during chemotherapeutic treatments.

In young patients with cancer, the options to preserve fertility are still limited and cryopreservation of one ovary is now a common procedure at pediatric cancer centers [5]. However, the options to use the preserved ovarian tissue are still experimental; transplantation of pieces of the cryopreserved ovarian cortex has resulted in the resumption of endocrine function and in live births but the procedure is only possible for those with low risk of preexisting contaminating cancer cells in the ovarian tissue. For others, in vitro maturation of eggs is an experimental process that has only been successful in animals so far. The use of GnRH agonist in pubertal girls has been discussed but is unlikely to have any effect [6]. Therefore, new approaches to protect gonadal tissues against the effects of chemotherapy are needed. The authors have observed that after cisplatin administration, p63 serves to eliminate the injured germ cells and that the kinase c-Abl is activated. Imatinib, an inhibitor of c-Abl, blocked the immediate appearance of apoptotic oocytes when delivered with cisplatin. Moreover, treatment of immature mice with imatinib and cisplatin resulted in normal-appearing follicles in adult ovarian tissue and restored fertility. As nicely discussed in the associated editorial [7], this breakthrough idea may raise several issues. First imatinib treatment might rescue damaged oocytes with a high risk for miscarriage and birth defects. Second, imatinib might modulate the effects of cisplatin on the target tumor, and there are some examples where it might increase or decrease the anticancer effect. Altogether, there is a need for more experimental data (action on the testis, effect on damage induced by other drugs than cisplatin) before we embark on clinical trials, but this first step is really good news.

Genetics, pathogenesis and clinical interventions in type 1 diabetes

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Type 1 diabetes is an autoimmune disorder afflicting millions of people worldwide. Once diagnosed, patients require lifelong insulin treatment and can experience numerous disease-associated complications. The last decade has seen tremendous advances in elucidating the causes and treatment of the disease based on extensive research both in rodent models of spontaneous diabetes and in humans. Integrating these advances has led to the recognition that the balance between regulatory and effector T cells determines disease risk, timing of disease activation, and disease tempo. The authors describe current progress, the challenges ahead and the new interventions that are being tested to address the unmet need for preventative or curative therapies.

Etiology of type 1 diabetes

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Recent genetic mapping and gene-phenotype studies have revealed the genetic architecture of type 1 diabetes. At least ten genes so far can be singled out as strong causal candidates. The known functions of these genes indicate the primary etiological pathways of this disease, including HLA class II and I molecules binding to preproinsulin peptides and T-cell receptors, T- and B-cell activation, innate pathogen-viral responses, chemokine and cytokine signaling, and T-regulatory and antigen-presenting cell functions. This review considers research in the field of type 1 diabetes toward identifying disease mechanisms using genetic approaches. The expression and functions of these pathways, and therefore disease susceptibility, will be influenced by epigenetic and environmental factors. Certain inherited immune phenotypes will be early precursors of type 1 diabetes and could be useful in future clinical trials.

Type 1 diabetes is among the most frequent conditions managed by pediatric endocrinologists and still has a very somber long-term prognosis despite advances in insulin delivery, glucose surveillance and patient education. It is also the pediatric endocrine disease on which the highest amount of research money has been spent, leading to major advances in our understanding of the mechanisms of the disease, but with limited impact on daily management. These two reviews are very timely and come from authorities in the field of diabetes genetics and immunology. They give an updated and comprehensive view on these fields and future research directions with the hope that these advances will improve patient care during the next decade.

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