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Abstracts

Adiponectin and Alzheimer's disease

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Adipokines could influence physiological processes including energy expenditure, insulin sensitivity and secretion, glucose and lipid metabolism and many others. Adiposity is associated with an unfavorable pattern of adipokines that results in enhanced morbidity of type 2 diabetes, hyperlipidemia, hypertension and cardiovascular disease. The role of metabolic disturbances and adiposity in the development of neurodegeneration found in Alzheimer's disease (AD), the main cause of memory impairment in elderly, has been discussed. T Interestingly, AD is characterized by the central functional hypoglycemia and hypometabolism. Insulin resistance occurring in the CNS of AD patients was named Type 3 Diabetes (T3D). Adiponectin possesses an anti-inflammatory and metabolism regulating properties. There is also a link between peripheral adiponectin activity and insulin/insulin resistance. Therefore, it seems to be important to assess whether adiponectin fractions in combination with metabolic parameters, especially insulin and insulin resistance, correlate with the stage of AD. Our data reporting changes in adiponectin profile in AD indicate a possible correlation between adiponectin variations and dementia. We hypothesize that these changes result from compensatory mechanism against neuropathological processes, as well as from adiponectin homeostasis impairment.

Adipsic diabetes insipidus in patient after resection of craniopharyngioma

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Introduction: Diabetes insipidus is common amongst patients after neurosurgery treatment of craniopharyngioma, and untreated leads to severe fluid and electrolyte imbalance.
We aim to present a case of adipsic diabetes insipidus after resection of craniopharyngioma.
57-years old woman after operation 1 year before, was admitted to the hospital due to recurrent hypernatremia, altered consciousness and psychomotor retardation. She had a multihormonal pituitary insufficiency. No history of polyuria and polydipsia was reported on desmopressin treatment (60 mcg every other day). The blood test showed serum Na concentration of 158 mmol/L, plasma osmolality 346 mOsm/kg, creatinine concentration 1,57 mg/dL. The patient was treated with fluids i.v., fluid balance monitoring was carried out. The dose of desmopressin was increased to 60 mcg twice a day. The patient was instructed to keep a low-sodium diet and drink an adequate amount of water. A significant improvement in the clinical status, normalization of sodium, osmolality, renal function were achieved. After discharge, frequent ambulatory visits were required.
To sum up, both polydipsic and adipsic diabetes insipidus in patients after craniopharyngioma treatment. Damage of the thirst center in the hypothalamus and abnormal thirst response to osmotic stimuli results in an absence of polydipsia and polyuria. An assessment of sodium concentration and plasma osmolality seem to be beneficial for this group of patients.

Suprasellar lipoma

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Introduction: Intracranial lipomas are congenital lesions found at any age. They represent less than 0.1% of all intracranial tumors. This kind of tumor could be asymptomatic or symptoms include epilepsy, headaches, behavioral changes, and cranial nerve paralysis.
We aim to present a case of suprasellar lipoma.
30 years old man with a suprasellar mass is under control of our Endocrinology Department. He had an MRI scan of the central nervous system because of severe headaches with fainting. MRI scan revealed the suprasellar tumor, 14 x 15 x 12 mm, described as a homogenous mass traversed by the small vessels, compressing the right half of the optic chiasm and pituitary stalk. At the time of diagnosis hormonal function of the hypothalamic-pituitary axis was intact. The patient showed a visual field defect with right-side temporal abnormalities. There was no indication for a neurosurgical intervention at that time. According to the MRI characteristics he was diagnosed with suprasellar lipoma. Because of no available evidence-based guidelines for the management of such rare suprasellar tumors, it was

decided to assess the patient's visual field and hormonal status every 6 months and MRI of the hypothalamic-pituitary region every 12 months. Up to date, the follow up has been continued for 30 months. The MRI scans revealed a stable image of the tumor. The patient did not show significant deterioration in the visual field, the hypothalamic-pituitary axis function was preserved.

Neuropeptide B stimulates insulin expression and secretion but not proliferation and cell death in INS-1E cells

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Introduction: Neuropeptide B (NPB) modulates appetite, body weight and energy homeostasis by interacting with G-protein coupled receptors termed as NPBW1 and NPBW2 (GPR7 and GPR8). Humans express both types of receptors, while rodents express NPBW1, only. NPB and NPBW1 are widely expressed in central nervous system and in peripheral tissues including pancreatic islets. Although recent animal studies revealed the prominent role of NPB and NPBW1 in controlling energy homeostasis and metabolism, the role of NPB in controlling pancreatic beta cell functions remain unknown.
The aim of this study was to characterize the effects of NPB on insulin expression and secretion in insulin producing INS-1E cells. Furthermore, the role of NPB in modulation of INS-1E cell proliferation, viability and death was evaluated.
The experiments were conducted on rat INS-1E cells (beta cell surrogate). Gene expression was assessed by real-time PCR. Cell proliferation and viability were determined by BrdU and MTT tests, respectively. Cell death was studied by evaluation of histone-complexed DNA fragments (mono- and oligonucleosomes).
The results of this study show that NPB stimulates insulin mRNA expression and secretion. By contrast, NPB fails to affect INS-1E cell proliferation, viability and death.
In conclusion, this data show that NPB may regulate energy homeostasis by stimulation of insulin neogenesis and secretion.

Olfactory neuroblastoma diagnosed in a patient with chronic syndrome of inappropriate antidiuretic hormone secretion

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The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is frequently related to malignancies. Most commonly it was reported in small cell lung cancer but association with many carcinomas and neuroendocrine tumours was described. To date, 18 cases of SIADH induced by olfactory neuroblastoma have been published. 27-year-old woman presented with 12-years history of severe hyponatremia in the course of idiopathic SIADH. She has been hospitalized many times because of recurrent symptoms (headache, nausea, vomiting, abdominal pain) of hyponatremia and hypoosmolality with high ADH level. She was treated with water restriction, furosemide, fludrocortisone or hydrocortisone. We performed further thorough examination and MRI revealed pathological mass in left nasal cavity and maxillary sinus. Patient suffered occasionally from epistaxis and nose congestion attributed to chronic sinusitis. 68Ga-DOTA-TATE PET/CT showed increased somatostatin receptor (SSR) expression in that mass. The biopsy result was olfactory neuroblastoma. The complete resection of the tumour that originated in ethmoid sinus was performed. She also received adjuvant radiotherapy. Immediately after surgery sodium concentration normalized and patient is normonatremic for almost 2 years since then. In all cases of SIADH thorough examination and searching for malignancy is essential. Even in long lasting idiopathic SIADH repeated imaging is necessary. SSR PET/CT could be helpful in such cases.

The effect of neurokinin A and B on *in vitro* prolactin secretion by anterior pituitary cells of cyclic gilts

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Introduction: Neurokinins participate in the regulation of reproductive functions, acting at three different levels of the hypothalamo-pituitary-gonadal axis. Our previous studies indicated that neurokinin A (NKA) and B (NKB) are synthesized in the porcine anterior pituitary and affect the expression of PRL, TRHR and D2R genes.
The aim of the current study was to determine the influence of NKA and NKB on *in vitro* prolactin secretion by porcine anterior pituitary cells during the estrous cycle. Cells isolated from anterior pituitaries of gilts on days 8–10, 15–16 and 18–20 ($n = 3 \times 5$) of the estrous cycle were incubated for 4 h with NKA and NKB (at doses 10–7, 10–8, 10–9 mol/L) alone or in combination with TRH or dopamine. Radioimmunoassay was performed to determine prolactin concentration in media collected after *in vitro* culture.
The results did not reveal any influence of NKA and NKB on basic prolactin secretion on examined days of the estrous cycle. However, we noted significantly

higher ($p < 0.05$) prolactin secretion on days 18–20 after treatment with NKB in combination with TRH. Furthermore, we observed a tendency ($p < 0.08$) to stimulation prolactin release by NKA in the presence of dopamine on days 15–16 of the estrous cycle.
In conclusion, presented data imply that neurokinins may be involved in the modulation of prolactin secretion at the pituitary level by affecting the responsiveness of lactotrophs to hypothalamic factors, involved in the control of its release, i.e. dopamine and TRH.

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Plasma omentin and visfatin in patients with systemic sclerosis — the preliminary investigation

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Introduction: Systemic sclerosis (SSc) is an autoimmune chronic disease characterized by vasculopathy and fibrosis of the skin and internal organs. The origin of this disease is still unknown but the latest studies showed a possible role of adipokines in the development of fibrosis in the course of SSc. Adipokines may act also as a modulator of the immune response and fibrosis.
The aim of our study was to evaluate the changes in plasma leptin levels of omentin and visfatin and HOMA-IR in patients suffering from SSc.
30 patients with SSc (age 51 ± 13; BMI 23.4 ± 2.9) and 12 healthy (age 35 ± 8; BMI 22.6 ± 2.8) were enrolled to the study. The severity of the skin fibrosis was evaluated using the Rodnan scale. In all participants, plasma omentin and visfatin were assessed using ELISA method as well as HOMA-IR was calculated.
Results: Plasma omentin levels and HOMA-IR were significantly higher in patients with SSc compared with control group. Patients with a duration of disease more than 10 years presented the highest levels of omentin. Omentin levels negatively correlated with the Rodnan scale. We did not notice the significant differences between patients with long-lasting SSc (> 10 yrs.) with respect to those who suffered less than 10 yrs. Our data did not reveal any changes in plasma visfatin levels.
To sum up, omentin may be a potential metabolic marker in a course of systemic sclerosis.

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BMP (*bone morphogenetic proteins*) system activity in the anterior pituitary gland

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Introduction: BMPs are secreted signaling molecules belonging to the transforming growth factor-β (TGF-β) superfamily known for its role in the regulation of anterior pituitary activity.
The aim of this study was to determine whether central (GnRH) and peripheral (17β-estradiol) affect selected BMPs transcription in anterior pituitary gland *in vivo*.
The experiment was conducted on ovariectomized 4 month old rats which received central (1 pulse/h/over 5h) microinjections of 1.5 nM GnRH; 2 nM GnRHR ant + 1.5 nM GnRH; 0.9% NaCl (controls) or, sc injections of 17β-estradiol (3x20 μg/0.2 mL), PPT (ESR1 agonist; 3x 0.5 mg/0.2 mL), DPN (ESR2 agonist; 3 x 0.5 mg/0.2 mL and in controls, 3 x 0.2 mL DMSO.
qRTPCR method was applied to evaluate BMP2, BMP4, BMP6, BMP7, BMP15, BMPRIA, BMPRIB, BMPR2, Smad1, Smad5, Smad8 mRNA expression.
The results indicated that GnRH up-regulated BMP2, BMP-15, and BMPR-IA mRNA expression as well as BMPs signaling pathway transcription factors Smad1 and Smad5 mRNA levels. Contrary, estrogen down-regulated BMPs system activity. A decreased BMP2 and BMP-6 mRNA level resulted from ESR1 stimulation whereas reduced BMP-15transcription required ESR1and ESR2 activity. BMPR-1A and BMPR2 mRNA level was diminished in an ESR1-dependent manner Both estrogen receptors promoted decrease of Smad5 transcription.
In conclusion, obtained data suggest that BMPs activity depends on GnRH and estrogenic inputs exerted in a gene-specific manner at the BMPs network transcriptional level.

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The diagnosis and treatment of pituitary insufficiency in adults

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Hypopituitarism is characterized by clinical symptoms of a deficiency of one or more hormones of the pituitary gland which can result from diseases of the pituitary gland or the hypothalamus. The prevalence of hypopituitarism 50 cases/100000 individuals probably underestimates the actual incidence, given that as many

as 30–40% of people with traumatic brain injury (TBI) might present impaired pituitary function. Mortality is increased by 1.3- to 2.2-fold compared with age- and sex-matched cohorts.
Hypopituitarism can be congenital or acquired. In adults the most common causes include intracranial tumors (including pituitary and hypothalamic tumors), neurosurgery, irradiation to head region, postpartum pituitary necrosis, cerebrovascular accidents, granulomatous or autoimmune hypophysitis, sarcoidosis and pituitary abscess. There is a growing evidence of the hypopituitarism found after TBI and other traumas including contact sports trauma (up to 49%), ischemic stroke (17%), patients with subarachnoid hemorrhage (up to 47%), surgeries eg. cardiosurgery or pituitary inflammation after new biological therapies. The clinical manifestations of hypopituitarism depend on the type and degree of hormone deficiency and the rapidity of its onset, may be non-specific and thus the diagnosis is often missed. The diagnosis of hypopituitarism is made by examining the basal hormone levels or performing stimulation tests in some cases. Replacement treatment exists in the form of thyroxine, hydrocortisone, sex steroids, growth hormone, and desmopressin. Modifications in replacement treatment are needed during the transition from pediatric/adolescence to adulthood, during pregnancy and stress/acute state.
The aim of the presentation is to present the current view on the diagnosis and treatment of pituitary insufficiency in adults illustrated by a clinical case presentation.

Diagnostics and management of growth hormone deficiency in childhood and adolescence — yesterday, today and tomorrow

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Growth hormone deficiency (GHD) is important cause of short stature in children with a prevalence of 1 in 4000 during childhood. The diagnosis of GHD is based on an assessment of auxological data with supporting evidence from biochemical and neuroradiological studies. Growth hormone (GH) stimulation tests play a key role in GHD diagnosis but the measured GH concentration can vary significantly with stimulation test and GH assay used creating difficulties for diagnostic accuracy. The lack of any gold standard test for GHD diagnosis has led to the development of somewhat arbitrary cut-off levels. When GH stimulation tests were first used, a peak GH after stimulation < 5 ng/mL was used to diagnose GHD. Over time the cut-off has increased to 7 ng/mL and 10 ng/mL. Separating the group of short children with mild GH deficiency from non GH deficient children remains challenging. In this presentation I will review the data from our department on diagnosis of GHD — which pharmacological test to use, issues with GH and IGF-1 assays. At the end of presentation are news about new trends in the therapy of GHD children with long acting GH molecules.

The effect of ACTH on the expression of gonadotropin-inducible ovarian transcription factor 1 (Giot1) gene in the adrenal glands of the rat

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Introduction: Giot1 belongs to the fast-responsive genes family. *In vivo*, in ovaries of immature rats, the expression of this gene increases rapidly after administration of PMSG or hCG. Moreover, *in vitro* levels of mRNA Giot1 in Leydig cells increase significantly after addition to the medium of pMSG/hCG. Detailed mutational studies of Giot1 proximal promoter have identified in this gene a cAMP response element (CRE).
The aim of the study was to demonstrate whether ACTH regulates the expression of Giot1 in adrenals and through which mechanism it exerts its effect.
Acute (1h) i.p. administration of ACTH to mature male rats causes a rapid increase in expression of the Giot1 gene in ZG and ZF/R. Similar results were obtained in the case of chronic infusion of ACTH. In both males and females, gonadectomy increases the expression of the gene in the adrenal glands. ACTH also stimulates the expression of the Giot1 gene in primary culture of rat adrenocortical cells. In contrast to ACTH, hCG does not affect both the level of expression of the Giot1 gene and corticosterone secretion. The stimulating effect of ACTH on the expression of the Giot1 gene is inhibited by administration of H-89. This suggests that the stimulating effect of ACTH on the expression of Giot1 gene is mediated by cAMP.
The obtained results suggest that Giot1 may be one of the factors involved in the regulation of adrenal steroidogenesis.

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The influence of melatonin and forskolin on the hypothalamic cAMP content as well as oxytocin secretion from the rat hypothalamus and neurohypophysis *in vitro*

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Introduction: The goal of the present investigation was to answer the question whether melatonin (MT) could influence the forskolin-induced accumulation of cAMP in the rat hypothalamus and oxytocin (OT) secretion from the rat hypothalamus (Hth) and neurohypophysis (NH) *in vitro*.

Material and methods: Male rats Hth and NH explants were separately placed in 1 mL of Krebs-Ringer buffer (K-RB). Each explant of Hth or NH was incubated successively in: 1 — normal K-RB {fluid F1}, 2 — the K-RB as F1 supplemented with melatonin (10^{-7} M) and/or forskolin (10^{-5} M) or their vehicles (0.1% ethanol or 0.1% DMSO) {fluid F2}. After 20 min incubation, each medium {F1 and F2} was collected and frozen before OT estimation by the RIA. At the end of incubation, the Hth samples were immediately placed in tubes containing 1 mL of 0.1 M HCl, frozen and stored at –20°C until the content of cAMP in the Hth was estimated by the ELISA assay.

Results: MT significantly diminished the cAMP accumulation and inhibited forskolin-induced elevation of the cAMP content in the rat Hth. Forskolin significantly increased OT secretion from the NH and Hth, while MT diminished basal and inhibited forskolin-stimulated OT release from the rat NH and Hth *in vitro*.

Conclusion: The present results suggest that melatonin employs the cAMP-dependent intracellular pathway(s) for its inhibitory influence on OT secretion from the rat Hth and NH *in vitro*.

This study was supported by Medical University of Lodz (grant No 503/6-103-01/503-61-001).

Neuroendocrine and metabolic response to critical illness

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Critical diseases are defined as any life-threatening conditions that require the maintenance of organ function in order to avoid an impending death. Without modern intensive care, the survival of critically ill patients is generally impossible. Critical diseases are an extreme form of hard physical effort. Biological reactions occurring in response to this condition are triggered immediately and on a larger scale than in other clinical conditions. Stress response (critical illness/life-threatening condition) involves the reaction of the endocrine system, including neuroendocrine and metabolic response. Due to intensive medical care, the survival of patients in previously fatal states has increased, but now more patients "enter" the chronic phase of critical illness, during which multi-week support/maintenance of organ functions is still necessary, despite the removal of factors initiating the critical illness.

The topic of the lecture includes: 1. the response of the hypothalamus and the anterior pituitary to the critical illness; 2. the response of the adrenal gland to life-threatening conditions; 3. NonThyroidal Illness Syndrome pathomechanism; 4. metabolic reactions (mainly, carbohydrate metabolism) that occur in critically ill patients. The lecture attempted to link the neuroendocrine and metabolic response to critical illness. Differences between its acute and chronic phase were taken into account.

The influence of all-trans retinoic acid on adiponectin and TNF-α levels in the adipose tissue of ApoE mice

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Introduction: Retinoids, which include naturally occurring vitamin A, are physiological regulators of a number of essential biological processes related to atherosclerosis including regulation of the lipid metabolism and inflammation.

The aim of the study was to examine the influence of all-trans retinoic acid (atRA) on adiponectin and TNF-α levels in the visceral and perirenal adipose tissue of ApoE mice.

Material and methods: Experiments were performed in 8 weeks old male mice: Apo-E (model of atherosclerosis) and C57BL/6J (control group) treated with vehicle (corn oil) or atRA for 8 weeks. AtRA or vehicle was administrated by the stomach tube. All animals were fed on the normal diet. Visceral and perirenal adipose tissue adiponectin and TNF-α concentrations were measured by enzyme-linked immunosorbent assay (ELISA).

Results: There was no significant difference between adiponectin concentrations in the visceral adipose tissue in all group of mice. However, TNF-α concentration was significantly lower in Apo-E mice treated with atRA than the vehicle. In the perirenal adipose tissue, adiponectin level was found to be markedly reduced and TNF-α concentration was significantly increased in C57BL/6J mice treated with atRA than the vehicle.
Conclusion: Our data suggest that atRA may reduce inflammation in the visceral adipose tissue of Apo-E mice. However, in the perirenal adipose tissue of C57BL/6J mice, atRA may increase pro-inflammatory cytokine-TNF-α and decrease adiponectin concentration.

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Non-functioning pituitary adenomas in a 5-year evaluation

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Introduction: Clinically non-functioning pituitary adenomas (NFPAs) are among the most common tumors in the sellar region, and their diagnosis is labor-intensive and cost-prohibitive and the immunohistochemistry does not always exhibit an actual lack of hormonal activity (null cell adenoma).
The aim of the study: Clinical, radiological, hormonal and immunohistochemical evaluation of patients with NFPAs.
Material and methods: 125 patients, mean age 50 ± 18.4, 77 women (61.6%) with diagnosed NFPAs, hospitalized in a period from June 2013 to May 2018 in the Clinic of Endocrinology, Medical University of Lublin.
A retrospective analysis of medical records of patients hospitalized due to NFPAs.
Results: In the radiological assessment, a predominance of macroadenomas (57.6%), median size 15.2 ± 11.3 mm, was observed. Most adenomas manifested with a compression of the intersection of optic nerves (40.7%), sphenoidal sinus invasion 39.8%, cavernous sinus invasion 19.5%, (multidirectional 28.8%). Clinically headache (45%), dizziness and visual disturbances (27% each) were observed. Additionally, in 30 (24%) patients pituitary insufficiency was found (gonadotropic 33.8%, corticotrophic and thyrotropic — 22%). In the 5-year follow-up, 23 (18.4%) patients underwent surgery, and the immunohistochemistry tests showed a dominance of null cells, gonadotropic cells and thyrotropic cells.
Conclusions: NFPAs are usually recognized as macroadenomas most commonly with coexisting suprasellar expansion and compression on the optic chiasm. Clinical manifestations were a headache in every second patient, and one in four presented hypopituitarism.

Visualizing migration and activation of T cells *in vivo*

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Multiple sclerosis (MS) is an autoimmune disease which is characterized by inflammation in the central nervous system (CNS). Although the detailed pathomechanism of MS is still largely unknown, autoantigen specific encephalitogenic T cells are considered as key player. To visualize how these T cells migrate into the CNS and induce inflammation, intravital imaging of these T cells in the animal model for MS, Experimental Autoimmune Encephalomyelitis (EAE) was performed by using intravital two-photon microscopy.
The imaging revealed that the T cells appeared in the blood vessels at the spinal cord leptomeninges before onset of clinical EAE. At this stage, the T cells migrated on the intraluminal surface of the vessels with integrin α4 dependent manner. After the extravasation beyond the Blood–Brain Barrier, the T cells contacted with phagocytes. Since the contact can induce T cell activation, which are known to be important to induce clinical EAE, T cells labelled with fluorescent protein based activation sensors were introduced to detect T cell activation in vivo. One is fluorescent resonance energy transfer (FRET) based calcium sensing protein, Twitch, and another is NFAT-GFP fusion protein. Both sensors successfully visualized T cell activation in vivo. Importantly, the intravital imaging is not applicable to only T cells but also other cell types, including neurons and glia cells.
In addition to observation of T cell migration and activation, the imaging can be used to evaluate therapeutic treatment. For example, the infusion of anti-integrin α4 antibody diminished intraluminal crawling within a few minutes and prevented clinical EAE completely. Indeed, similar antibody is used in MS patients and show beneficial effect. In addition, the application of anti-MHC class II blocking antibody or inhibitor of intracellular calcium signalling prevented T cell activation and ameliorated clinical EAE, revealing that T cell activation is critical check point to induce CNS inflammation. Therefore, intravital imaging is very powerful tool to directly visualize cellular motility and function *in vivo* to understand the biological events as well as to develop therapeutic treatment.

Abnormalities involved in intracellular growth signal transduction

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Introduction: In recent years more and more attention has also been paid to irregularities in promoters of particular genes as the ones which are potentially responsible for the incorrect generation of signal factors. There is continuous search for irregularities of genes coding promoter and regulatory factors. Additionally, the focus is more frequent on the role of carrier proteins, such as GHBP and IGFBP. It is considered that a proper gene coding and maintaining right developmental stage--dependent concentrations, which results from normal regulation of biosynthesis, is necessary for proper functioning of carrier proteins. This is tightly related to specific nucleotide composition of promoter and regulatory regions. Improper binding of transcription factors can be a cause of low or high concentrations of carrier proteins, which in significant way will disturb time of growth hormone action, for example, IGF-I. It is connected with the recently emerging possibilities of treating also those patients in whom short stature was the result of molecular defects.
Results of studies indicate that there is an indisputable necessity of broadening the molecular diagnostic basis in Poland.

Spexin as a modulator of body weight, metabolic and hormonal profile in obese rats

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Introduction: Spexin (SPX) is a novel, very conservative 14 amino-acids peptide discovered in 2007 using bioinformatics methods. SPX arises as a result of post--translational modifications of a prepropeptide, which is composed of 116 amino acid residues. It was showed that SPX negatively correlates with insulin resistance and could be involved in regulation of food intake behavior, neuroendocrine and metabolic functions.
The aim of the study was to investigate the effect of 7 days SPX (35 μg/kg b.w.) administration on body weight, metabolic and hormonal profile in obese rats.
We found that short term SPX administration decreased body weight ($p < 0.05$) and increased insulin sensitivity in rats ($p < 0.01$). Moreover, we noted that spexin decreased serum level of ghrelin (active and total) ($p < 0.05$) and leptin ($p < 0.05$). Simultaneously, SPX increased glucagon ($p < 0.05$) and triiodothyronine ($p < 0.01$) concentrations in blood serum. Study of the metabolic profile showed that SPX decreased triglycerides level ($p < 0.01$). We did not find any effect of SPX on cholesterol and non-esterified fatty acids levels. Moreover, we investigated the effect of SPX on ALT, AST, GGTP and ALP activity in blood serum. We noted that SPX reduces the activity of investigated enzymes.
These data indicate that spexin is a novel relevant player in regulation of body weight and metabolism. Our results suggest that SPX may be further evaluated as a potentially promising therapeutic target.

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All you need to know about the genetics of pituitary adenomas

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While just a few years ago we rarely thought about genetics when looking after pituitary patients, now this aspect of endocrinology, similar to many others, is keeping the genetic labs increasingly busy. Pituitary adenomas with genetic origin can present as part of syndrome, such as MEN1&4, Carney complex, McCune-Albright syndrome, DICER1 syndrome and SDH-related syndrome, but most often they present as isolated disease as part of Familial Isolated Pituitary Adenoma (FIPA). In the FIPA group currently three genes have been described. (1) Heterozygous germline mutations in the aryl hydrocarbon receptor interacting protein *(AIP)* gene lead of young-onset mostly growth hormone or mixed growth hormone/prolactin-secreting pituitary adenomas. Due to the low (~20%) penetrance almost half of the *AIP* mutation positive patients do not have a known family history and present as a seemingly sporadic case. (2) X-linked acrogigantism (XLAG) — duplication of the orphan G protein coupled receptor *GPR101* gene, located on the X the chromosome, leads to infant-onset GH excess usually with concomitant hyperprolactinaemia. Interestingly while girls, who represent 80% of the known cases, usually have germline mutation, boys mostly have somatic mosaicism. (3) More recently a few cases of Cushing's disease have been described with mutation in the *CABLES1* (Cdk5 and Abl enzyme substrate 1) gene, although the importance of this gene needs to be confirmed. The majority of the FIPA families, however, have no know genetic mutation

and further studies are needed to identify the diseases causing genes in these kindreds.
Search for somatic mutations were most successful in somatotrophinomas with *GNAS* mutations in upto 40% of cases, and in corticotorph adenomas with upto 30% (50% in females) of *USB8* mutations.
But what is the point to identify the disease causing genes in patients with genetic form of pituitary adenomas? In syndromic diseases it may help to search for other manifestation of the disease; characteristics of the disease may help to decide on the appropriate treatment modalities; family members can be screened and followed for early diagnosis, which is a crucial point in the successful treatment of pituitary adenomas; patients often react remarkably positively learning the genetic origin of their disease, it gives them a long-sought explanation for the "why me?" question. Finally, establishing novel pathways could lead to disease-specific treatment in the future.

Endoscopic endonasal treatment of Rathke cleft cysts — clinical series

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Introduction: Rathke's cleft cysts (RCCs) are benign sellar and suprasellar lesions arising from epithelial remnants of Rathke's pouch. The symptomatic cases are treated surgically.
The aim of the study is to evaluate endoscopic endonasal approaches in the management of RCCs.
Material and methods: The study is a retrospective clinical series analysis**.** We retrospectively analyzed a series of 71 patients complaining of a RCC, operated with endoscopic transsphenoidal approach at the Department of Neurosurgery Center of Oncology in Warsaw In all cases the transsphenoidal endoscopic approach was performed. In 7 cases the extended approach was utilized.
Simple cyst evacuation was possible in all cases, in 10 patients (15%) the tumor capsule was resected. In rest of the patients the evacuation of cyst was followed by capsule fenestration and biopsy of tumor capsule, some maneuvers to prevent it recollection. In 7 cases (10.1%) the extended transtuberculum sellae approach was used to resect suprasellar RCC.
Results: In 52 (72%) patients RCC symptoms resolved. The visual performance improved in 12 out of 15 cases with visual degradation. The most frequent complication was transient diabetes insipidus in 12 cases (16.7%), permanent DI was observed in 3 cases (4.1%). There was 1 case of cerebrospinal fluid leak. During the median observation time of 29 months recurrence/regrowth occurred in in 6 patients (8.4%), only 3 cases needed reoperation for symptomatic recollection.
Conclusions: The endoscopic endonasal transsphenoidal approach for the removal of a symptomatic RCC is safe and effective method of treatment. The modification of the approach to the so called "extended" approach, allows surgical treatment of isolated suprasellar RCCs eliminating the need for transcranial approach.

Limited–extended trans tuberculum approach for non-complex suprasellar hypothalamo-pituitary pathologies — case series

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Introduction: The extended endoscopic approaches for suprasellar pathologies gained place in neurosurgical armamentarium for suprasellar pathologies.
The aim of the study was to analyze results and complications of extended transtuberculum/transplanum transsphenoidal approach modification called limited--extended approach. The modification consisted of limitation of approach to one nostril approach with no conchectomy and without use of nososeptal flap. The opening of the dura of suprasellar area was limited to sufficient minimum. The closure was performed with 2 flattened fat tissue grafts augmented with collagen matrix and buttressed with titanium mesh wedged in bone defect.
The study is a retrospective analysis of the use of limited extended suprasellar approach in 13 patients with different non-complex pathologies not demanding extra space for microdissection: 5 cases of suprasellar Rathke cleft cysts, 3 cases of infundibular tumors, 2 suprasellar pituitary adenomas, one meningioma, one chordoma, and one case of optic chiasm glioma.
Results: the complete resection was achieved for all except optic chiasm tumor, there was a case of permanent diabetes insipidus after resection of infundibular tumor. There was no CSF leaks, the healing of nasal cavity was checked after 4 weeks, only one case showed prolonged healing with chronic sinusitis. There was no nasal morbidity, no septal perforation.
The extended approach without flap and binostril approach can be advocated for selected non complex pathologies with like suprasellar cysts and small solid tumors not invading dural margins. The limitation of surgical freedom from limited exposure is not relevant in those pathologies. Moreover the nasal cavity healing was significantly shorter and nasal complications were fewer.

Clinico-pathological study of invasive macroadenomas with infrasellar direction of invasion

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Introduction: Invasion of neighboring anatomical structures is a major factor limiting surgical efficacy. The infrasellar tumor invasion is regarded as one of factors for clinically aggressive course for adenoma. The purpose of the study was clinico-pathological evaluation of invasive pituitary adenomas with infrasellar invasion.
Results: Of 1072 pituitary adenomas treated at Oncological Center from 2010 to 2017, 115 (10.8%) were reported as invading either: sellar floor or sphenoid sinus or clivus. Adenomas with infrasellar invasion comprised 29% of invasive pituitary adenomas (115/378). Thirty five of the cases with infrasellar invasion were diagnosed as giant adenomas (> 4 cm). Most of the cases with infrasellar invasion were among non functioning pituitary adenomas 67.5% (gonadotrophs-68, null cell adenomas 4, silent ACTH 3, silent GH 3). The infrasellar invasion coexisted in 55% (63/115) with invasive growth into parasellar or suprasellar areas. Selective infrasellar invasion was observed in 21out of 115 cases (18%) what makes 5.5% of all invasive adenomas. Infrasellar invasion limited effectiveness of surgical treatment in comparison to other invasive tumors (21% vs 35%) Fisher exact test 0.008.
Conclusions: Infrasellar invasion is most often coexisting with other directions of invasive growth. Isolated infrasellar growth is rare and in majority of cases observed in prolactin secreting and non functioning adenomas. The infrasellar direction of invasion if a negative factor for surgical resection.

Partial agenesis of corpus callosum in a patient with craniopharyngioma — a very rare case of the co-occurrence of two diseases or a congenital syndrome?

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The aim of the study is to present a complex case of overlap between two rare congenital central nervous system diseases of an opposite nature (atrophy and proliferation) in a patient with pituitary insufficiency after previous surgical treatment due to craniopharyngioma.
Case report: A 35-year-old man with a disease diagnosed at the age of 15. The first symptom of the tumor was increased intracranial pressure with a headache, nausea and vomiting. The patient was twice operated (1997, 2002). After the second neurosurgery, persistent multi-hormonal hipopituitarism occurred, requiring chronic hormonal substitution. Then he developed metabolic syndrome with morbid obesity (BMI = 40.2 kg/m^2), diabetes and dyslipidemia. Only three years ago the agenesis of two thirds of the corpus callosum together with the asymmetric ventricular system with the dominance of the left lateral ventricle of the brain was detected during MRI. Throughout the treatment period, the patient was reluctant to cooperate, showed lack of understanding of his own health situation, complained about family and medical staff and had an unrestrained appetite. These behaviors were interpreted as the effect of post-operative damage to the hypothalamus.
Conclusion: Difficulties in the interpretation of symptoms resulting from surgery and/or concomitant agenesis of the corpus callosum complicate the assessment of the clinical picture and treatment results in our patient.

Long-term subclinical Cushing's disease in patient with corticotroph macroadenoma — case report

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The aim of the study is to present a clinical picture of a long-lasting subclinical Cushing's disease in patient with corticotroph macroadenoma.
Case report: 5 years ago in a 62-year-old patient the mass (24 x 33 x 28 mm) of the irregular shape located in the Turkish saddle was visible. The hormonal studies revealed: ACTH 104.1 pg/mL (n < 63.6); normal cortisol diurnal rhythm and normal cortisol urine excretion but no inhibition neither during 1mg DXM nor during both phases of Liddle's test. He underwent an incomplete transsphenoidal adenomectomy. In postoperative examination pituitary adenoma GH(–), PRL(–), ACTH(+), TSH(–), FSH(–), LH(–), alpha-subunit(–), MIB < 3% and in an electron microscope the sparsely granulated adenoma was found. After surgery, normal ACTH and proper pituitary function persisted for 22 months. Then a slight increase of ACTH was observed. One year later

ACTH increased to 86.3 pg/dL, the lack of the daily cortisol rhythm together with the lack of inhibition during 1mg DXM test and in MRI progression of the tumor residue were observed. 4 years after surgery ACTH 111.8 pg/mL, cortisol without circadian rhythm and further progression of tumor size were revealed. Currently ACTH is 136.5 pg/mL, cortisol circadian rhythm is incorrect, daily urine cortisol excretion is normal and tumor size in MRI 25 x 23 x 26 mm, but there are no evident clinical signs of hypercortisolemia until now.

Conclusion: Subclinical Cushing's disease caused by pituitary corticotropic macroadenoma may be clinically elusive for many years.

Pituitary tumors resistant to medical treatment: molecular and clinical aspects

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Despite the inhibitory effects on tumor growth and hormone secretion of DA agonists and somatostatin analogs (SSa), 10% of patients with PRLoma and 30–40% of acromegalic patients are resistant to cabergoline and to SSa, respectively. Generally, a reduced expression of functional DA and SS receptors in pituitary tumors has been associated with a poor response. In particular, this event has been clearly demonstrated in PRLomas. Conversely, though *in vivo* GH suppression and tumor shrinkage induced by SS analogs correlates with SSTR2 expression, some GHomas are resistant to therapy despite high SSTR2 expression. The molecular events responsible for reduced DRD2 and SSTRs expression are still largely unknown. In particular, while no mutation of the DRD2 gene has been found in resistant PRLomas, DA-resistance has been correlated only to a common DRD2 gene polymorphism. Interestingly, it has been recently demonstrated that filamin-A (FLNA), a widely expressed cytoskeleton protein with scaffolding properties, is crucial for D2R expression and signaling in lactotrophs, suggesting that the impaired response to DA may be related to the reduction of FLNA expression in DA-resistant PRLomas. Few data are available on possible DRD2 signal transduction alterations. In particular, it has been demonstrated the downregulation of TGF-β/Smad pathway in DA-resistant PRLomas compared to normal human anterior pituitaries. Similarly to DRD2, no mutations of SSTR2 and SSTR5 genes are usually found in resistant patients. Though polymorphic variants in SSTR2 gene seem to have no role in determining SS resistance of GHomas, a single SSTR5 gene polymorphism predisposes to resistance to antiproliferative effects of SS, increased aggressiveness, and post-surgical reoccurrence of pituitary tumors. Finally, the expression of a truncated variant of SSTR5 has been found to correlate with SS-resistance and tumor invasiveness possibly having a dominant-negative effect on SSTR2-mediated signaling.

Analysis of disorders of carbohydrate metabolism associated with newly diagnosed acromegaly

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Introduction: Acromegaly is a rare endocrinopathy characterized by excessive production of hGH, with a corresponding increase in IGF-1 concentration. Both hGH and IGF-1 exhibit antagonism towards hypoglycemic action of endogenous insulin, leading to states of carbohydrate disorders.

The aim of the study was a retrospective analysis of the occurrence of carbohydrate metabolism disorders in patients with newly diagnosed acromegaly.

Material and methods: Retrospective analysis of available medical data of patients hospitalized in the Department of Endocrinology in 10 years period. The evaluation included 40 patients with newly diagnosed acromegaly before introduction of long-acting somatostatin analogue therapy.

Results: 40 patients were included in the study: 24 women and 16 men (60% vs 40%), 53.3 ± 11.8 years, BMI 31.6 ± 5.8 kg/m^2 with mean IGF-1 740.9 ng/mL (Me: 638.7). The carbohydrate disorders in the form of IFG were diagnosed in 17 patients (42.5%), IGT in 5 patients (12.5%) (double pre-diabetic status IFG+IGT in 3 patients). Diabetes most likely secondary to acromegaly was observed in 9 patients (22.5%). The mean HbA1c in the DM group was 5.8%.

Conclusions: IFG was the most common carbohydrate disorder associated with acromegaly. Carbohydrate metabolism disorders were not seen only in every third patient with newly diagnosed acromegaly. Co-occurring diabetes minimizes the utility of the key diagnostic test used in acromegaly: 75 g glucose hGH suppression.

Cyclic variant of ACTH-dependent Cushing's syndrome. A case study

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Introduction: Cushing's cyclic syndrome is characterized by hypercortisolemia phases alternating with normocortisolemia, provided that no treatment has been introduced. Epidemiological data are not consistent, estimating the frequency of a cyclic variant as 15–36%.

Case report: A 42-year-old female patient with ACTH-dependent Cushing's syndrome due to microadenoma, with typical phenotypic and metabolic features (secondary hypertension and insulin resistance). She was diagnosed 22 years ago (abnormal "fixed" daily rhythm of cortisol with elevated levels of cortisol). In the head CT performed at that time (October 25, 1995), the pituitary microadenoma was described, though no further diagnostic procedures were continued nor any treatment introduced. Many times the exacerbation of "cushingoid" symptoms with their gradual resolution were observed, despite lack of specific treatment. New MRI scan shows pituitary microadenoma (7 x 5 mm). Double hormonal evaluation, performed currently, one month apart, managed to capture the state of hypercortisolemia with subsequent normalization of cortisol.

Conclusions: The possibility of a cyclic variant of Cushing's syndrome should be suspected in every patient with inconsistencies between clinical presentation and the results of the adrenocorticotroph axis evaluation. The cyclic Cushing syndrome is characterized by a less dynamic capacity to generate complications of hypercortisolemia, than does the classic form of the syndrome.

Myokines, factors that increase the tissue insulin sensitivity

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Introduction: Skeletal muscles account approximately for 40–50% of the total body weight, therefore constitute the largest organ in the human body. Exercise possesses positive benefits for the body composition, insulin sensitivity, cardiovascular health and cognition. Moderate exercise has been shown to increase lifespan in rats, improve neuromuscular and neurological performance in mice, and to reduce hyperglycemia, hypercholesterolemia and hypertension. Proteins expressed and released by contracting muscle that have autocrine, paracrine, and endocrine bioactivities are termed myokines. Interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-15 (IL-15), brain-derived neurotrophic factor (BDNF), leukemia inhibitory factor (LIF), fibroblast growth factor 21 (FGF21), irisin and myonectin (CTRP15) are amongst them. IL-6 can play an important role in the regulation of a low-grade inflammation generated during obesity. Muscle-derived IL-15 could play a role as an important mediator of anti-adipogenic and insulin-sensitizing effects of the endurance exercise.

The aim of our study was to determine the effect of IL-15-myokine on omentin and chemerin secretion from the rat adipose tissue explants.

Our results clearly showed that IL-15 resulted in enhanced expression and secretion of omentin and decreased secretion of chemerin from the adipose tissue explants culture.

Conclusions: Regular physical activity may be an important strategy to prevent progression of insulin resistance associated with metabolic disease. Moreover, regular physical activity contributes to a reduction of the visceral fat amount and improves tissue insulin sensitivity.

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Neuroendocrine mechanisms in pathophysiology of heart failure

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Heart failure (HF) is a disease of ageing populations. Its prevalence increases with age and exceeds 10% in subjects above 70 years of age. Ischemic heart disease, including myocardial infarction and hypertension, are the most common causes of HF. They result in myocardial remodeling, reduced cardiac output and inadequate organs perfusion and in consequence signs and symptoms including dyspnea, edema and reduced exercise capacity.

Pathophysiology of HF is complex but chronic neuroendocrine activation (NEA) involving mainly activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) is its principal factor. Furthermore, vasopressin release and synthesis of endothelins, proinflammatory cytokines and natriuretic peptides are enhanced.

Physiological concept behind NEA is to maintain cardiovascular homeostasis under stress. Reduced number of functional cardiomyocytes as a result of ischemia or

hypertension triggers NEA as a compensatory mechanism. Indeed, SNS and RAAS activation initially acts to maintain cardiac output by increasing contractility, heart rate, the circulating blood volume and constricting resistance arterioles.
However, NEA is programmed by the evolution for short term regulation and an organism is helpless when faced with negative effects of its prolonged action. If the detrimental or stressing stimulus for the cardiovascular system persists, adverse effects of long term NEA appear: hypertrophy, dilatation of cardiac chambers, fibrosis, arrhythmias as well as cellular and molecular remodeling. Indeed, chronic SNS and RAAS activation was shown to result in HF progression and eventually death.
An important confirmation of key role of NEA in the HF pathophysiology is provided by the fact that current pharmacological treatment of HF that reduces mortality and slows the disease progression, involves restoration of the neuroendocrine balance through reduction of SNS overactivity, RAAS blockade at several levels and recently also through blockade of an endopeptidase that breaks down natriuretic peptides.

Blood serum concentrations of gonadotropins in patients with gonadotropinomas in relation to the immunoreactivity of pituitary adenoma

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Introduction: Although the active gonadotropin-secreting pituitary adenomas are considered as very rare, the vast majority of pituitary tumours diagnosed as „nonfuctioning" express gonadotropins or their free β or α subunits. However, the systemic investigations comparing the serum concentrations of folitropin (FSH), lutropin (LH) and α-subunit (α-SU) before surgery with the immunoreactivity of the respective substances in the excised tumours are still lacking.
Material and methods: Immunostaining of FSH, LH and α-SU was compared in 43 surgically removed gonadotropin — expressing pituitary adenomas with serum concentrations of the above mentioned substances before surgery in the same patients.
Results: The serum concentrations of FSH were elevated (> 10 mU/mL) in 8/12 (66.7%) cases of FSH-positive adenomas. In contrast, in FSH-negative tumours the elevation of FSH is absent. Moreover, only 1/25 (4%) patient with LH-positive adenoma had the elevated serum concentration of LH (51.5 mU/mL). The oversecretion of LH was observed neither in adenomas expressing free β LH nor in LH-negative tumours. In patients with α-SU-positive adenomas the elevated serum levels of α-SU (> 1 mU/mL) were observed in 3/15 (20%) cases. No α -SU elevations were observed in patients with α-SU-negative adenomas.
Conclusions: Although „silent" gonadotropinomas constitute a frequent subtype of pituitary adenomas, the „active" (i.e. manifesting by gonadotropin excess) are rare (approx. 4% of all pituitary adenomas). Gonadotropinomas are difficult to diagnose before surgery. The measurement of gonadotropins including α-SU is needed but often not sufficient for presurgical diagnosis.

Nesfatin-1 is a novel modulator of stress response in rat

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Nesfatin-1 is distributed in the stress-related brain regions including the hypothalamus and co-localized with stress-related hormones. It is also involved into regulation of over-feeding and modulation of obesity status often accompanied by inflammation. The objective of the study was to investigate whether the stressful immune-inflammatory response is a factor involved into association between nesfatin-1 and pituitary-adrenal axis in rat. Experiment was carried out on male Wistar rats divided into control, naltrexone, mannan and naltrexone+mannan treated groups. The immune status was estimated by the Il-6 level and leucocytes number, stress reaction was measured by blood ACTH level and corticosterone concentration in the adrenal gland. The involvement of nesfatin-1 in the stress response was evaluated by the changes of this peptide level in the blood and hypothalamus. Mannan, serving as a proinflammatory factor, significantly increased the leucocytes number and Il-6 plasma level. Increased level of plasma ACTH in parallel with decreased concentration of corticosterone in adrenal gland proved the presence of stress response. Plasma level and hypothalamic concentration of nesfatin-1 reached the highest values 120 min after mannan injection. Interestingly, nesfatin-1 showed higher response also to the naltrexone, an opioid receptor

antagonist, what may suggest interaction of this peptide and opioids. Thus, the reaction of nesfatin-1 to the inflammation suggests its important role in the regulation of stress response at the central and peripheral levels. The hyperactivity of pituitary-adrenal axis associated with higher level of nesfatin-1 after naltrexone injection clearly indicates the opposite effect to the opioids regulation of stress reaction.

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Subclinical left ventricular systolic dysfunction in patients with naive acromegaly assessed by two-dimensional speckle tracking echocardiography (2D-STE)

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Introduction: Speckle tracking echocardiography (STE) is a novel method that allows for the study of global longitudinal strain (GLS), a marker of early and subclinical left ventricular (LV) systolic dysfunction.

The aim of the study: To evaluate left ventricular GLS in patients with naive acromegaly with normal LV systolic function.

Material and methods: Fifty-one consecutive patients with naive acromegaly with normal systolic LV function measured by ejection fraction (EF), and a control group were matched for age and gender underwent 2D-STE.

Results: The mean GLS was lower in acromegalics than in the controls (in%, –17.28 ± 4.9 vs. –20.9 ± 3.2, $p < 0.01$). Majority of acromegaly patients (60.7%) had abnormal GLS. Patients with impairment in GLS had longer duration of acromegaly symptoms compared to those with normal GLS values (years, 10.0 vs. 5.0, $p < 0.05$). Acromegalics with lower GLS had also an increase in parameters of LV thickness i.e. IVS [in mm, 13 (8–19) vs. 11.5 (8-14), $p < 0.05$] and PW [in mm, 13 (8–17) vs. 12 (9–13) $p < 0.05$]. There was a negative correlation between LVMi and GLS ($R = –0.38$, $p < 0.01$).

Conclusions: Naive acromegalic patients presented with lower GLS compared to the control group which indicates subclinical systolic dysfunction in the untreated acromegalic patients. We found longer disease duration in acromegalics with impairment in GLS compared to those with normal values.

Cushing's disease with cyclic occurrence of hypercortisolemia — a case report

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Introduction: Cyclic Cushing's syndrome is characterized by alternating periods of hypercortisolemia and episodes of normal serum cortisol. The clinical picture may be ambiguous, which can cause difficulties in the diagnosis.

The aim of the study: Presentation of the diagnostic process of a patient with cyclic Cushing's syndrome.

A case report: 28 year old female with metabolic syndrome (giant obesity, type 2/secondary diabetes, insulin resistance, hypertension, mixed hyperlipidemia, hyperuricemia), hyperandrogenism and hypercortisolemia observed in an outpatient setting. During many hospitalizations, hypercortisolemia, an inverted circadian rhythm of ACTH secretion and 3–6 times increased excretion of cortisol in the 24-hour urine sample were observed. In the dexamethasone suppression tests, there was no suppression by low dose and full suppression by 8 mg dexamethasone. In the pituitary MRI, a focal lesion was described in the intermediate lobe (a small mucous cyst of the Rathke pouch or a cystic microadenoma). In a second study, the correct response to 2 mg dexamethasone was observed, and pseudo-Cushing syndrome was excluded with the CRH test. Periodic occurrence of cortisolemia and the results of functional tests, along with clinical symptoms and medical imaging, allowed for the diagnosis of cyclic Cushing's syndrome most likely caused by a pituitary adenoma. The patient was referred for Inferior petrosal sinus sampling.

Conclusions: Differential diagnosis of Cushing's syndrome is often complicated. Diverse medical signs of patients with cyclic Cushing's syndrome, especially periods with normal cortisol levels, may lead to incorrect diagnoses.

BDNF — a central modulator of the GnRH/LH axis activity

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Introduction: Neuropeptides involved in the regulation of food intake are often involved in the reproductive processes activity controlling. Brain-derived neurotrophic factor (BDNF) (belonging to neurotrophins

peptides family) is engaged in appetite regulation processes at the central nervous system level.
The aim of this study was to verify the research hypothesis, which assumes that BDNF can modulates the gonadotrophic axis secretory activity at the hypothalamic-pituitary level in sheep.
Material and methods: The experiment was performed on Polish Merino sheep (n = 24). Animals were divided into 3 groups and infusions into the III ventricle of the brain was performed: 1. Ringer-Locke solution 480 μL/day; 2. BDNF in dose 10 μg/480 μL/day; 3. BDNF in dose 60 μg/480 μL/day. After the last infusion sheep were slaughtered, the selected structures of the brain and plasma samples were stored for Real Time RT qPCR and radioimmunoassay analysis.
Results: The obtained results showed that BDNF stimulate the expression of GnRH gene in the POA as well as GnRH-R in the pituitary. Exogenous BDNF stimulate also the LH gene and protein expression in the gonadotrophic pituitary cells. These changes led to increase in LH level in the blood plasma.
Conclusions: Based on the presented results it can be concluded that BDNF may modulate the gonadotrophic axis activity in sheep.

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Transcriptome analysis of rat adrenocortical cells exposed to ACTH *in vitro* and *in vivo*

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The aim of the study was to analyse the expression of ACTH-stimulated adrenocortical cells genes in three experimental models: (1) primary adrenocortical cell culture (exposure for 24 h), (2) acute (1h) i.p. ACTH injection and (3) prolonged ACTH infusion for 48 h using microosmotic pumps. Studies were carried out using Affymetrix Rat Gene 2.1 ST Arrays. Obtained raw data were analyzed using bioinformatics tools based on the R programming language. The selection criteria of a significantly affected genes were based on a fold expression change > 1.5 and 10% FDR. The total number of DEG was distributed as follows: *in vitro* (up — 1180, down — 417 genes), *in vivo* 1h (up — 534, down — 485 genes), *in vivo* 48 h (up — 49, down — 53 genes). In order to demonstrate general similarities and differences in ACTH action on adrenal cells in the studied models, principal component analysis (PCA), correlation matrix and Venn diagram were performed. DEG sets were assigned to significantly enriched ontology terms using DAVID and GSEA bioinformatics tools.
Our results confirm that ACTH causes very dynamic changes in transcriptional profile in rat adrenocortical cells. In case of acute administration of ACTH *in vivo*, these changes are similar to those observed *in vitro*. However, after prolonged infusion of ACTH, the transcriptional profile of adrenocortical cells changes significantly. Under these conditions, the number of differentially expressed genes is significantly lower.

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Maternal brain adaptations in pregnancy to satisfy fetal needs and risk of adverse programming

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Successful pregnancy requires adjustments to multiple maternal homeostatic mechanisms governed by the maternal brain, to support survival, growth and development of the conceptus and placenta. Such adjustments constitute allostasis (stability or survival through change), and have a cost: allostatic load. In pregnancy allostasis is driven by ovarian, anterior pituitary, placental and feto-placental hormones acting on the maternal brain: e.g. relaxin stimulates vasopressin secretion, permitting blood volume expansion; prolactin (and placental lactogens) induces leptin resistance, increasing appetite and energy supply; allopregnanolone (AP, 5α-reduced neuroactive progesterone metabolite), reduces hypothalamo-pituitary-adrenal (HPA) axis responses to stressors, conserving energy and protecting fetuses. AP is produced and acts in the nucleus tractus solitarii where 5α-reductase gene (*srd5a1*) expression increases in pregnancy. Here, AP induces opioid inhibition of noradrenergic input to the stress axis, with up- or down-regulation of key neuropeptide and receptor genes. The expression of hundreds more genes is altered in the maternal brain in pregnancy. Allostatic changes in gene expression in the brain evidently involve epigenetic mechanisms (e.g. DNA methylation/demethylation, histone modifications, or micro (mi)RNAs — which regulate *srd5a1* expression). There is sparse information about epigenetic changes in the maternal brain in pregnancy, but abundant data about epigenetic changes from early-life experience in offspring brains.

Many women carry an existing allostatic load into pregnancy, due to socio-economic circumstances, or obesity. These pregnancies have poorer outcomes, suggesting negative interactions between pre-pregnancy and pregnancy allostatic loads: a bad start for a new life. Importantly, exposure of pregnant rats to a social stressor results in F1 offspring with abnormal metabolic and stress response phenotypes. Pregnancy in such F1 programmed females, without further stress, results in F2 progeny with abnormal stress responses. It will be necessary to probe gene expression changes, and epigenetic mechanisms in brains of F1 vs normal pregnant rats to gain insights into intergenerational transfer of programming.

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Prediction of growth hormone (GH) therapy effectiveness in children with GH deficiency — application of neural models

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Accurate prediction of growth hormone (GH) therapy effectiveness is an important issue in pediatric endocrinology. Multiple linear regression and empirical non-linear models have been previously used for this purpose. Artificial neural networks (ANN) allow detection of both linear and non-linear dependencies without assuming their character a priori. Neural models consist of input layer to which input (explanatory) variables are delivered, hidden layers that process the data and output layer which outputs the result of prediction. Among various ANN, multilayer perceptron presented to be optimal for prediction of response to GH therapy. Two models were constructed for children with GH deficiency (GHD): predicting change in height SDS during 1st year of treatment and predicting final height (FH) SDS. Starting from 17 (1st year model) and 20 (FH) potential predictors, input cancellation algorithm reduced their number to 9 and 10 significant ones. Eliminated variables included GH peak after falling asleep and in stimulation tests, while IGF-I concentrations and earlier growth were the most important predictors. Average error of prediction was 0.25 SD (1st year) and 0.50 SD (FH); both models explained about 45% of variability. Majority of the dependencies among variables were non-linear. Neural models allow to obtain accurate height prediction for children with GHD, to select significant predictors and to provide realistic, personalized expectations about treatment effects.

Modelling anorexia nervosa in rats

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Introduction: Anorexia nervosa (AN) is an eating disorder characterized by weight loss and difficulties in maintaining an appropriate body weight. Rodents show a tendency to self-starvation when exposed to a time-restricted feeding schedule and given the possibility of voluntary physical activity in a running wheel, and thus mimic AN.
The aim of the study was to establish the model of activity-based anorexia (ABA) in our laboratory investigating food intake, running wheel activity and body weight in rats. Only female rats were used due to the higher prevalence of anorexia in females compared to males.
Material and methods: Wistar rats weighing 170–220 g upon their arrival were housed in groups under controlled conditions and were fed with standard rat chow (Labofeed B, Kcynia, Poland) and tap water *ad libitum*. This study was carried out in accordance with the institutional guidelines (65/2017). After an initial acclimatization period of 5 days, rats (n = 32) were randomly assigned to one of four groups (n = 8 each) with: (1) no extra activity + *ad libitum* feeding schedule, (2) voluntary activity in a running wheel + a*d libitum* feeding schedule, (3) no extra activity + restricted feeding schedule, and (ABA group) voluntary activity in a running wheel + restricted feeding schedule. All cages contained environmental enrichment and bedding material, and were placed adjacent to each other to provide sight, acoustic and odor contact. Body weight, food intake and activity were monitored daily. The experiment was discontinued and animals euthanized when the body weight loss exceeded 25%.
Results: ABA rats showed a reduced daily food intake and a significant reduction in body weight in comparison to other groups. Physical activity was also significantly increased in ABA rats in comparison to a voluntary activity in a running wheel + a*d libitum* feeding group.
Conclusions: The ABA model combines voluntary physical activity in a running wheel and time-restricted feeding to reduce body weight. Our data point the usefulness of the model to understand pathophysiological alterations occurring in AN.

Profiling of miRNA expression in sheep hypothalamus after BDNF treatment

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Introduction: Brain-derived neurotrophic factor (BDNF) is growth factors protein, exhibiting neuromodulatory action on the whole brain and may participate in modulation of the metabolic processes at the CNS level. Moreover, available studies have shown that BDNF participate in pathophysiological mechanisms of many diseases which disturb the body energy homeostasis. Because BDNF modulate the activity of NPY/AgRP and CART/αMSH neurons — which create hypothalamic appetite–regulating centre, the aim of study was to profiling the expression of selected miRNAs (involved in post-transcriptional modulation of NPY, AgRP, CART and POMC mRNA expression) in hypothalamus.
Material and methods: The experiment was performed on Polish Merino sheep (n = 24). The following types of infusion into the third brain ventricle was performed: 1. Ringer-Locke solution 480 μL/day; 2. BDNF in dose 10 μg/480 μL/day; 3. BDNF in dose 60 μg/480 μL/day. After the last infusion sheep were decapitated and MBH was dissected to determine the expression of selected miRNAs.
Results: The presence of all investigated miRNAs in MBH from all experimental groups was confirmed. A dose dependent changes in: miRNA-33b-5p, miRNA-647, miRNA-647, miRNA-377-3p, miRNA-214-3p, miRNA-485 expression was observed.
Conclusions: Summarizing BDNF may modulate selected miRNAs expression which one could be involved in post-transcriptional regulation of NPY/AgRP and CART/αMSH neurons activity.

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Prolactin/adenoma maximum diameter ratio as a predictor of clinical phenotype of prolactinomas and dopamine agonists treatment response — 5-years observation of a single-centre

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Introduction: Prolactinomas are the most common hormone secreting pituitary adenomas and they constitute 40% of all pituitary tumors. So far, there are not clinical, biochemical and imaging criteria with sufficient predictive value for evaluation of their clinical phenotypes and response for dopamine agonists treatment.
The aim of this retrospective study was to explore the connection between prolactin/adenoma maximum diameter (PRL/MD) ratio and clinical phenotype of prolactinomas at the diagnosis and after treatment.
Material and methods: 68 patients (38 male), aged 17–78 years with newly diagnosed prolactinomas hospitalized in the Department of Endocrinology, Medical University of Lublin, between May 2013 and May 2018 were retrospectively analyzed. 17 patients had microprolactinoma and 51 macroprolactinoma. The correlation between PRL, PRL/MD ratio and hyperprolactinemia-related symptoms, adenoma mass effects and hypopituitarism were evaluated.
Results: It has been observed that the initial value of the PRL/MD ratio did not affect the change in tumor size after treatment. Such a relationship has been demonstrated only in case of initial levels of PRL ($p = 0.015$) and the dose of bromocriptine ($p = 0.031$). There was statistically significant correlation between the PRL/MD ratio and occurrence of symptoms of prolactinomas such as sexual dysfunction ($p = 0.015$) and fatigue ($p = 0.004$). PRL/MD ratio was strongly positively associated with a dose of DA during follow-up period.
Conclusions: The results suggest that prolactin/adenoma maximum diameter ratio may predict clinical phenotype of prolactinomas better than baseline prolactin level and tumor size separately. However, analyzed group of patients is too small to achieve significance. Therefore, further studies are necessary.

Neural networks as a tool for prognosis of the results of therapies

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Neural networks become very popular as a tool for modelling of numerous systems — technological, economical, sociological, psychological and even political. On the other hand neural networks are models of neural structures and neural processes observed in real brain. However, for modelling of real neural structures and real neural processes occurring in living brain neural networks they are too simple. Nevertheless neural networks can be used for modelling behavior of many biological systems and structures. Such models are not useful for explaining biological systems and processes but can be very useful for analysis of such systems' behavior including prognosis of future results of selected

activities, e.g., prognosis of results of different therapies for modelled illnesses. In this paper general information about neural networks principles, structures, functions, learning and applications are presented. Practical use of neural network as a tool for particular application (prediction of growth hormone therapy effectiveness) will be presented in next paper by Dr. Urszula Smyczynska. In this paper only the general methodology of such modelling is presented. Thanks to this, the content contained in this paper can be used by many doctors to predict the effects of many different therapies. Most important factors, determining success of every neural network application, are selection of input data for the model, designing od proper neural network type and structure, collecting learning set, performing the learning process, and wise interpretation of answers given by the network. All such items will be discussed in the lecture.

Influence of pituitary gonadotropins, prolactin and growth hormone on expression of AQP5 in the porcine ovarian follicular cells

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Introduction: Aquaporins (AQPs) are proteins integrated with the cell membranes that form selective channels to water and other molecules.

The aim of the present study was to examine the effect of luteinizing hormone (LH), follculotropic hormone (FSH), prolactin (PRL) and growth hormone (GH) on AQP5 expression in granulosa (Gc) and theca (Tc) cells.

Material and methods: The cell culture were incubated with experimental factors. Gene and protein expression was evaluated by qPCR, Western blot and immunofluorescence. All numerical data were analyzed by one-way ANOVA and Tukey post hoc test.

Results: The results showed that GH decreased expression of Aqp5 in Gc from middle follicles in relation to control. Increased expression of Aqp5 in Tc from large follicles was indicated by GH and PRL in relation to control. Significantly higher expression of AQP5 protein in Gc from middle and large follicles was indicated by FSH and PRL in relation to control. In co-cultures increased expression of Aqp5 was observed in Gc from large follicles incubated with LH, PRL and GH in relation to control. Significantly increased expression of Aqp5 was observed in co-cultures of Tc from all type of follicles incubated with LH, whereas PRL stimulated expression of Aqp5 in Tc from middle-sized follicles.

Conclusions: These present results, has provided some novel insights into the regulation of AQP5 present in granulosa and theca cells of porcine ovarian follicles, suggest that pituitary gonadotropins, PRL and GH may mediate the action of AQP5.

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The effect of anandamide on LH secretion from sheep anterior pituitary explants — *ex vivo* study

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Introduction: Cannabinoids as well as endocannabinoids (ECBs) interfere in the neuroendocrine control of reproduction influencing GnRH/LH secretion. Besides the effect in the hypothalamus, still controversial is the direct activity of ECBs on the pituitary.

The present study was designed to determine the effect of endocannabinoid — anandamide (ANA) on LH secretion from the anterior pituitary (AP) explants collected from anestrous ewes.

Material and methods: The *ex vivo* experiment was carried out on the tissues collected from adult, 3-year old, Blackhead ewes (n = 6) in anestrous period. The AP were dissected and divided into 4 explants. The explants from each ewe were treated with: 1) M199 only, 2) GnRH, 3) ANA and 4) GnRH + ANA and incubated for 3 h at 37°C (87% O_2, 5% CO_2). The LH concentration in collected medium was assayed by RIA method and LHβ gene expression in the AP explants by Real-Time PCR method. Data were analyzed using the two-way ANOVA followed the Fisher's least significance test.

Results: The results clearly showed that in the AP explants GnRH treatment stimulated ($P < 0.05$) the LHβ gene expression and in the explants co-incubated with GnRH, anandamide suppressed ($P < 0.05$) stimulatory effect of GnRH on the LHβ gene expression. The anandamide treatment also suppressed ($P < 0.05$) the stimulatory effect of GnRH treatment on LH release.

Conclusions: These *ex vivo* results suggest that endocannabinoid anandamide may influence reproductive processes acting at the pituitary level suppressing LH secretion.

Immunohistochemical detection of somatostatin and dopamine receptors in pituitary adenomas from patients with acromegaly

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Introduction: In acromegaly, pharmacotherapy is an important additional, or sometimes alternative, method of treatment for the surgical removal of the pituitary tumor. Nowadays, in accordance with recommendations, long-acting somatostatin analogues acting mainly via somatostatin receptor type 2 are used as first-line drugs. Sometimes, agonists of dopamine D2 receptor (DR2) are applied. However, some patients with acromegaly are resistant to these drugs. So for effective treatment, an exact profile of the receptors present in pituitary adenomas is needed, as well as other medications.

The aim of the study was to identify the somatostatin and dopamine receptors in pituitary tumors from patients with acromegaly.

Material and methods: Specific receptor antibodies were used to immunohistochemically determine the expression of all somatostatin receptors (SSTR1-5), and dopamine DR2 and DR4 receptors, in 21 pituitary tumors. DR4 belongs to the family of D2-like receptors and has a partially homologous structure to DR2.

Results: SSTR1 expression was noted in 18 tumors, SSTR3 in 17 and SSTR5 in 16. SSTR2 was detected in only 14 samples. No SSTR4 expression was observed. A positive reaction with anti-DR2 antibodies occurred in seven tumors, and a reaction to anti-DR4 antibodies in 14 samples. In two cases negative for SSTR2, the dopamine D2 receptor was observed. Moreover, one case demonstrated a positive reaction with anti-DR4 antibodies, but no reaction with any somatostatin receptors or DR2. Both somatostatin and dopamine receptors exhibited cytoplasmic or membrane localizations.

Conclusion: The lack of somatostatin receptors and the presence of dopamine receptors in pituitary tumors justifies their treatment with dopamine agonists. However, the influence of DR4 expression on the effectiveness of dopamine agonists requires further detailed studies. The immunohistochemical evaluation of somatostatin and dopamine receptors in pituitary adenomas may allow appropriate pharmacological therapy to be chosen in patients with acromegaly.

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Valproate (VPA and levetiracetam (LEV) affect gonadotrope genes mRNA expression in anterior pituitary gland of rat *ex vivo*

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Introduction: VPA and LEV a potent antiepileptic drugs has been claimed to induce reproductive disturbances in man. Although mechanisms responsible for VPA and LEV effects on reproductive axis activity are not fully recognized, existing data suggest both gonadal and hypothalamo-pituitary sites of VPA and LEV action. In previous study we reported that both drugs suppressed only GnRH — stimulated but not the basal LH release from anterior pituitary cells *in vitro*. VPA was reported to repress CnRHR-1 transcription in GnRH neuronal GT1-7 cell-line and inhibited synthesis of GnRH.

The aim of the study was to determine whether VPA and LEV modulate GnRHR, LHβ, FSHβ mRNA expression in anterior pituitary gland of rat *ex vivo*.

The experiment was conducted on anterior pituitary explants from the anterior pituitary of male 3 month-old the rat. Explants were stimulated for 3h with GnRH (1 μM), VPA (10 mM), LEV (10 mM) GnRH + VPA, GnRH + LEV. Total RNA was isolated according to standard methods and specific genes mRNA expression was assessed using qRT-PCR method. The reference gene was GAPDH.

Results: VPA and LEV inhibited the GnRH-stimulated increase of GnRH-R and FSHβ mRNA expression whereas stimulated the expression of mRNA for LHβ mRNA were significantly elevated in response to VPA and LEV treatment.

Conclusion: VPA and LEV antiepileptic drugs specifically affect transcriptional gonadotropic activity via direct action exerted at the pituitary level.

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Expression of dopamine receptors 4 in clinically nonfunctioning pituitary adenomas

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Introduction: Clinically non-functioning pituitary adenomas (CNFPA) are tumors that do not induce clinical symptoms of hyperpituitarism or any increase in the level of pituitary hormones. The pharmacological treatment of CNFPA is used when contraindications for surgery or recurrence of the tumor occur. Currently, somatostatin analogs are applied, or sometimes the dopamine agonists bromocriptine or cabergoline acting through the dopamine receptor 2, are used but their effectiveness is insufficient. Recently, dopamine receptors 4 (DR4) have been identified in normal cells of pituitary; these belong to the D2-like receptor family and are partially homologous to DR2. However, as the presence of DR4 in malignant cells has only so far been described in isolated cases. The present study investigates the occurrence of DR4 receptors in clinically non-functioning pituitary adenomas (CNPA).

Material and methods: Thirty-nine human clinically hormonally-inactive pituitary adenomas were examined. The immunohistochemical evaluation identified the following hormonal phenotypes for the tumors: 18 plurihormonal adenomas, 17 gonadotropinomas, two corticotropinomas, one thyreotropinoma and one *null-cell adenoma*. DR4 were visualized by immunohistochemistry using rabbit polyclonal anti-human antibody.

Results: Positive immunostaining to DR4 was shown in 33/39 pituitary adenomas. Dopamine receptors were located in the cell membrane, as well as in the cytoplasm of tumor cells. Among plurihormonal adenomas, a positive reaction for the anti-DR4 antibody (most often membrano-cytoplasmic) was observed in 16/18 cases and in gonadotropinomas, positive immunostaining (more commonly cytoplasmic) was found in 14/17 tumors. In other adenomas, DR4 occurred only in the cytoplasm.

Conclusion: Our studies have shown that CNFPA cells possess DR4 both in the cell membrane and in the cytoplasm. However, to determine whether the expression of DR4 may improve the effectiveness of pituitary adenomas pharmacotherapy, such as the currently used dopamine analogues, further detailed studies are needed.

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Central injection of neostigmine diminishes lipopolysaccharide-induced suppression of GnRH/LH secretion in ewes during the follicular phase of the estrous cycle

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The study was designed to determine whether the central injection of neostigmine, reversible inhibitor of acetylcholinesterase (AChE), will suppress lipopolysaccharide (LPS)-induced synthesis of interleukin (IL)-1β in the hypothalamus and reduce the effect of immune stress on gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) secretion.

Material and methods: The *in vivo* experiment was performed on 4 groups (n = 6) of ewes: control (saline, i.v.), neostigmine-treated (1 mg/animal, i.c.v.), LPS-treated (400 ng/kg, i.v.), and neostigmine- (i.c.v.) and LPS- (i.v.) treated during the synchronized follicular phase. The animals were injected with neostigmine/Ringer's solution 0.5 h prior to LPS/saline treatment and then euthanized 3 h after LPS/saline treatment. The concentration of LH in blood was assayed by RIA. The content of GnRH in the hypothalamus was determined by ELISA. The gene expressions of GnRH, LHβ, IL-1β and IL-1 receptors were assayed by Real-Time PCR.

Results: Neostigmine injection not only abolished suppressive effect of LPS on GnRH and LH secretions, but animals injected with LPS and neostigmine showed higher circulating level of LH in competition to control group. At least partially, this effect of neostigmine treatment may result from inhibition of IL-1β synthesis in the hypothalamus.

Concluding, the study showed that central injection of neostigmine effectively diminished the negative effect of inflammation on GnRH/LH secretion in ewes.

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BDNF — possible action on the somatotrophic axis activity

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Introduction: Brain-derived neurotrophic factor (BDNF) is one of the growth factors protein belonging to neurotrophins peptides family. Neuromodulatory action of BDNF at the CNS level is connected with the regulation of the metabolic and energy intake processes. Therefore it is probable, that BDNF can participates in the regulation of growth and development processes which are dependent on the organism energy status.
The aim of this study was to verify the research hypothesis, which assume that BDNF can modulate somatotrophic axis activity in sheep.
Material and methods: The experiment was performed on sexually mature Polish Merino sheep (n = 24). Animals were divided into 3 groups. The following intracerebroventricular infusions were performed: control group (Ringer-Locke solution), group I (BDNF in dose 60 μg/480 μL/day), and group II (BDNF in dose 10 μg/480 μL/day). After the experiment animals were slaughtered and the selected structures of the hypothalamus, pituitaries were stored for Real Time RT qPCR. Central infusion of BDNF evoked the dose-dependent changes in srif and ghrh mRNA expression.
Results: The obtained result show an increase in SRIF mRNA expression in AHA and in GHRH mRNA expression in MBH. Moreover, changes in Gh, GHRH-R, SRIF-R mRNA expression in the pituitary cells were noted.
Conclusions: The results obtained so far suggest that BDNF is engaged in growth processes regulation at the central nervous system level.

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Association between thyroid-stimulating hormone and metabolic parameters in euthyroid patients with polycystic ovary syndrome

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Introduction: Polycystic ovary syndrome (PCOS) is characterized by oligo- or anovulation, hyperandrogenism and insulin resistance. Moreover, it is associated with higher risk of diabetes mellitus and dyslipidemia. Some data also suggest higher prevalence of autoimmune thyroid disorders in PCOS patients.
The aim of the study: To assess the relationship between thyroid-stimulating hormone (TSH) levels and metabolic parameters in euthyroid patients with PCOS.
Material and methods: The study enrolled 28 euthyroid patients with diagnosed PCOS on the basis of Rotterdam criteria. Exclusion criteria were: history of thyroid disorders, diabetes mellitus, hyperprolactinemia, Cushing's syndrome, congenital adrenal hyperplasia, pregnancy and medications that can alter TSH levels or lipid profile. Lipid profile and oral glucose tolerance test with calculation of HOMA index were performed in each case. PCOS patients were divided according to TSH concentrations into 2 subgroups: subgroup A — low normal range TSH (0.27–2.49 μIU/mL) and subgroup B — high normal range TSH (2.5–4.2 μIU/mL).
Results: Subgroup A was characterized by lower levels of low density lipoproteins, triglyceride and higher levels of high density lipoproteins than subgroup B. Moreover, lower levels of fasting insulin were observed in subgroup A compared to subgroup B. Fasting glucose concentrations were comparable in both subgroups while HOMA index was significantly lower in subgroup A (1.69 ± 0.23 vs. 2.02 ± 0.28).
Conclusions: Upper normal limit TSH concentration is associated with worse lipid profile and higher insulin resistance index in euthyroid PCOS patients. Therefore, a cut-off value for TSH < 2.5 μIU/mL should be established for PCOS patients, especially for those with other risk factors of cardiovascular diseases.

The role of somatostatin analogues and dopamine agonists in the postsurgical management of non-functioning pituitary adenomas

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Introduction: Surgery, which remains the first-line treatment of invasive non-functioning pituitary adenomas (NFPA), is rarely curative, leaving tumour remnant that can regrow in a significant proportion of cases. Postsurgical management of NFPA is not clear, however, some data suggest that somatostatin analogues (SSA) and dopamine agonists (DA) could be effective in preventing residual tumour progression.
The aim of the study: To assess the efficacy of SSA and/or DA on tumour volume and visual field (VF) in patients with NFPA after incomplete surgery.
Material and methods: Twenty-eight patients not cured by surgery were treated with either SSA (8 patients

— octreotide 20 mg intramuscular or lanreotide autogel 120 mg subcutaneously every 28 days), DA (10 patients — bromocriptine 2.5–5 mg daily or cabergoline 1–2 mg weekly) or with combined therapy with SSA and DA. The presence of somatostatin receptors in scintigraphy and immunohistochemistry was a sine qua non condition to start SSA therapy. The follow-up period varied from 18 months to 20 years. Adenoma size was evaluated in pituitary magnetic resonance imaging while VF tests were assessed by experienced ophthalmologists.

Results: We observed tumour progression in respectively 22.2% patients treated with SSA and 40% patients given DA. None of these patients showed regression of the adenoma. Considering combined therapy, tumour progression was noticed in 33.3% cases, however, 22.2% patients achieved tumour shrinkage. Enlargement of tumour size was associated with VF deterioration, albeit tumour shrinkage did not correspond to VF improvement.

Conclusions: DA are not more effective than SSA in the postsurgical management of NFPA. However, combination of both agents seems to be the most effective strategy, giving hope for tumour shrinkage in some cases.

Tumour progression in clinically non-functioning pituitary adenomas — does somatostatin analogue therapy decrease the risk?

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Introduction: The management of clinically non-functioning pituitary adenomas (NFPA) remains a debated issue. Surgery, which is indisputably indicated in invasive NFPA, is rarely curative. Moreover, it is not always feasible due to potential complications or contraindications. Expression of somatostatin receptors (SSTR) form the rationale for the use of somatostatin analogues (SSA) in NFPA.

The aim of the study: To compare the risk of NFPA progression in patients treated with SSA vs. those without pharmacotherapy.

Material and methods: 57 patients with NFPA (subgroup A-40 after incomplete surgery + subgroup B-17 not operated) were enrolled into the study. SSTR scintigraphy and additionally immunohistochemistry (subgroup A) were performed. The presence of SSTR was confirmed in 25 patients (17 from subgroup A+8 from subgroup B) in whom SSA therapy was started (every 4 weeks: octreotide LAR 20 mg intramuscular or lanreotide autogel 120 mg deep subcutaneous injection). The duration of the therapy varied from 16 months to 18 years. Adenoma size was estimated in pituitary magnetic resonance imaging.

Results: Tumour progression rate was twice higher in patients who were not treated with SSA (71.9% vs. 36%). In subgroup A tumour volume increased in 35.3% patients treated with SSA compared to 74% those without pharmacotherapy. Moreover, in subgroup B tumour progression was noticed in 37.5% SSA treated patients vs. 66.7% not SSA treated patients.

Conclusions: SSA significantly decrease the probability of tumour progression in NFPA, however, further studies should be carried out.

What is new in acromegaly?

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Acromegaly is a rare chronic disease caused by growth hormone hypersecretion (GH), mostly (99%) by pituitary adenomas (> 70% macroadenomas). Acromegaly leads to altered appearance (enlargement of the facial bones, hands and feet), bones, soft tissues and internal organs hyperplasia, and many comorbidities which result in reduction in length and quality of life. In percent of cases acromegaly has genetic causes: multiple endocrine neoplasia type 1, Mc-Cune Albright syndrome, familial acromegaly and Carney's syndrome, aryl hydrocarbon receptor interacting protein gene mutations, X-LAG caused by microduplications on chromosome Xq26.3 encompassing the gene GPR101. In those cases the course of the disease is altered, with mostly aggressive tumours, which often do not respond to pharmacological treatment. The biochemical confirmation of acromegaly includes GH and IGF-1 assays. However, in ¼ patients there are discrepancies, due to the occurrence of heterophile antibodies, or anti-GH and anti-IGF-1 antibodies which cause difficulties in the interpretation of the results. Treatment of acromegaly includes surgery, radiotherapy and medical treatment (somatostatin analogues, pegvisomant, dopamine receptor agonists). While 1st generation somatostatin analogues are effective in 40 percent cases, it comes out that a new agent: 2nd generation somatostatin analogue, pasireotide, is effective in 20 percent patients who do not respond to 1st generation somatostatin analogues. Pasireotide has affinity for many somatostatin receptors, especially SSTR5.

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The effect of the hypothalamo-pituitary-adrenal hormones on adiponectin gene expression during inflammation in *in vitro* condition

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Introduction: It is recognized that the adipose tissue produces multiple peptides, called adipokines, which play a significant role in the pathogenesis of a low-grade inflammation associated with obesity and metabolic syndrome. Also, they are involved into regulation of chronic inflammatory and autoimmune diseases. Among variety of adipokines, adiponectin is proposed as important anti-inflammatory mediator. Chronic stress characterized by prolonged alteration in the hypothalamo-pituitary-adrenal (HPA) axis and additionally combined with positive energy balance, may be a contributor to the increased risk for obesity.

Thus, the present study aimed to examine the effect of exogenous HPA hormones on the expression of adiponectin in the cultured adipocytes during inflammation induced by TNF-alpha.

Human adipocytes cultured in specific medium were treated with CRH, ACTH and glucocorticoids alone or together with TNF-alpha for 24 h, than the adiponectin mRNA was expressed quantitatively by real-time PCR. TNF-alpha alone strongly increased adiponectin mRNA levels after 24 h ($P < 0.01$). Both hormones, CRH and ACTH, increased adipokine mRNA expression, in contrast glucocorticoids did not changed the adiponectin expression. Interestingly, in TNF-alpha presence HPA hormones decreased expression of adipokine after 24 h ($P < 0.01$).

Obtained results indicate, that the effect of stress hormones on the synthesis of adiponectin in adipocytes depends on inflammatory status.

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