VI ZJAZD

POLSKIEGO TOWARZYSTWA NEUROENDOKRYNOLOGII

18–19 listopada 2022
Łódź

Organizatorzy:

PTNE

WYDZIAŁ BIOLOGII i OCHRONY ŚRODOWISKA
Uniwersytet Łódzki

Polskie Towarzystwo Endokrynologiczne

Polskie Towarzystwo Fizjologiczne

CENTRUM MEDYCZNE
KSZTAŁCENIA PODYPLOMOWEGO

UNIWERSYTET ROLNICZY
im. Hugona Kołłątaja w Krakowie

Patronat
– Rektor Uniwersytetu Rolniczego w Krakowie

Honorowy Patronat
– Rektor Śląskiego Uniwersytetu Medycznego w Katowicach

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Sponsorzy:

IPSEN
Innovation for patient care

RECORDATI POLSKA
GROUP

Szanowni Państwo,

Mam zaszczyt zaprosić Państwa na VI Zjazd Polskiego Towarzystwa Neuroendokrynologii oraz V Łódzkie Spotkania Przysadkowe organizowane przez Polskie Towarzystwo Neuroendokrynologii przy współudziale naukowców ze znamienitych jednostek naukowych krajowych i zagranicznych.

Podczas Sympozjum satelitarnego - V Łódzkich Spotkań Przysadkowych, przedstawione zostaną problemy związane z nowoczesnymi metodami leczenia akromegalii i guzów przysadki. W sesji neuroendokrynologii doświadczalnej zostaną wygłoszone wykłady z zakresu psychoneuroendokrynologii. W sesjach klinicznych wykłady będą dotyczyć leczenia choroby Cushinga, otyłości, unikatowej roli wazopresyny oraz analogów hormonów o właściwościach neuroprotekcyjnych. Ukoronowaniem tych tematów będzie wykład poświęcony osobniczej wrażliwości na działanie wirusa Covid-19.

Dzięki hybrydowej formie Zjazdu, interesującym sesjom wykładowym, posterowym oraz panelom dyskusyjnym, Uczestnicy będą mieć możliwość czynnego włączenia się w obrady poprzez zadawanie pytań i dyskusję nad wieloma problemami związanymi z neuroendokrynologią.

Wierzę, że informacje przedstawione i przedyskutowane podczas Zjazdu będą przydatne dla wszystkich zainteresowanych poznaniem najnowszych osiągnięć neuroendokrynologii doświadczalnej i klinicznej - naukowców, nauczycieli i studentów z wielu ośrodków naukowych.

Zjazd odbędzie się w formie hybrydowej – w siedzibie Uniwersytetu Łódzkiego oraz za pośrednictwem platformy TEAMS udostępnionej przez Uniwersytet Łódzki, szczegóły dotyczące zgłoszenia, rejestracji, program oraz pozostałe informacje zamieszczone są na stronie ZjazduVIzjazdPTNE.biol.uni.lodz.pl

Niezależnie od wybranej formy uczestnictwa warto spotkać się na VI Zjeździe PTNE w Łodzi, mieście wielu kultur i unikatowych zabytków.

Z wyrazami szacunku,
Krystyna Pierzchała-Koziec
Prezes Polskiego Towarzystwa Neuroendokrynologii

BOOK OF ABSTRACTS

Scientific Committee

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Computer specialist Michał Gruberski (Łódź)

Prof. dr hab. Kazimierz Kochman

(1938 - 2020)

Życie i działalność naukowa

Alina Gajewska[1], Marek Pawlikowski[2]
1 Instytut Fizjologii i Żywienia Zwierząt im. Jana Kielanowskiego PAN, Jabłonna.
2 Profesor emerytowany Uniwersytetu Medycznego w Łodzi.

Kazimierz Ernest Kochman urodził się 18 maja 1938 roku w miejscowości Bajdy k. Krosna. Jego rodzicami byli Andrzej i Józefa z d. Zajchowska. Studia odbył w latach 1956 - 1961 na Wydziale Biologii i Nauki o Ziemi Uniwersytetu Warszawskiego, na kierunku biochemia, uzyskując tytuł magistra nauk biologicznych ze specjalnością biochemia. Pracę naukową rozpoczął na stanowisku asystenta w Katedrze Biochemii Uniwersytetu Warszawskiego, kierowanej przez prof. Irenę Chmielewską. W 1962 roku, po spotkaniu z profesorem Eugeniuszem Domańskim, jednym z najwybitniejszych pionierów neuroendokrynologii eksperymentalnej w Polsce, podjął pod jego kierunkiem pracę badawczą w nowo utworzonym Instytucie Fizjologii i Żywienia Zwierząt PAN w Jabłonnie. Fascynacja zainicjowanymi i stale rozwijanymi badaniami aktywności układów neuroendokrynnych towarzyszyła profesorowi Kazimierzowi Kochmanowi nieprzerwanie przez 51 lat pracy naukowej w Jabłonnie. Stopień doktora nauk przyrodniczych uzyskał w roku 1969 na podstawie rozprawy doktorskiej przygotowanej w Instytucie pod kierunkiem prof. Eugeniusza Domańskiego i obronionej w Wyższej Szkole Rolniczej w Krakowie. W tym samym roku objął stanowisko adiunkta w Zakładzie Neurofizjologii i Endokrynologii Instytutu. W roku 1978, po kolokwium habilitacyjnym w Instytucie Biochemii i Biofizyki PAN w Warszawie, uzyskał stopień naukowy doktora habilitowanego nauk biologicznych ze specjalnością biochemia, w roku 1979 objął stanowisko docenta wraz z kierownictwem utworzonej wówczas w Instytucie w Jabłonnie Pracowni Neurohormonów. Tytuł naukowy profesora oraz stanowisko profesora w Instytucie otrzymał w 1989 roku. W latach 2004 -2007 pełnił funkcję zastępcy dyrektora Instytutu d/s naukowych.

Bardzo ważnym aspektem aktywności zawodowej profesora Kochmana były Jego badania naukowe prowadzone w Laboratoire des Hormones Polypeptidiques CNRS w Gif-Sur -Yvette we Francji, w National Institute of Aging w Baltimore w USA, a także w National Institute of Advanced Industrial Science and Technology w Tsukuba w Japonii. Rozpoczętą w latach siedemdziesiątych XX w. współpracę z ośrodkiem francuskim kierowanym przez profesora Mariana Jutisza, a następnie przez profesora Raymonda Counisa kontynuował do 2010 roku. Do końca pracy zawodowej utrzymywał też kontakt z kilkoma ośrodkami w Japonii. Wyrazem uznania dla pracy badawczej profesora Kazimierza Kochmana były kilkukrotnie przyznawane nagrody indywidulane i zespołowe

prezesa PAN; a także Złoty Krzyż Zasługi otrzymany w 2005 roku.

Działalność naukowa prof. Kochmana ogniskowała się na problemach regulacji funkcji układu podwzgórzowo-przysadkowego, ze szczególnym uwzględnieniem aktywności neurohormonu gonadoliberyny (GnRH) będącego podwzgórzowym regulatorem biosyntezy i uwalniania gonadotropin (LH i FSH) z komórek gonadotropowych przedniego płata przysadki. Już w latach sześćdziesiątych XX w., mając do dyspozycji jedynie 5000 podwzgórz owczych, uzyskał w Instytucie w Jabłonnie preparat, który po częściowym oczyszczeniu scharakteryzował jako substancję zawierającą wiązania aminokwasowe, o masie cząsteczkowej ok. 1300 -1400 kDa, odporną na gotowanie i o strukturze chemicznej pozbawionej mostka dwusiarczkowego. Po podaniu in vivo preparat ten zaindukował owulację u owcy. Ostateczne określenie struktury pierwszorzędowej dekapeptydu uwalniającego gonadotropiny dokonało się w 1971 roku w dwóch niezależnych ośrodkach badawczych kierowanych przez prof. Andrew Schally'ego (USA) oraz Rogera Guillemina (Francja). Ich osiągnięcie zostało uhonorowane nagrodą Nobla w dziedzinie fizjologii i medycyny przyznaną w 1977 roku „za odkrycia dotyczące produkcji hormonów peptydowych w mózgu". Dalsze badania profesora Kochmana dotyczyły m.in. mechanizmów biosyntezy GnRH w podwzgórzu, jak też przysadkowej aktywności kinaz białkowych zależnych od cAMP i tubuliny. Szczególnie znaczące okazało się opracowanie przez Niego oryginalnej metody izolacji i oczyszczania prolaktyny z przedniego płata przysadki. Wysokooczyszczone preparaty prolaktyny owczej, bydlęcej i świńskiej przyniosły ogromne uznanie profesorowi, który przez wiele lat przekazywał je w postaci daru do badań prowadzonych w renomowanych ośrodkach w Polsce i na świecie. Kontynuując badania nad fizjologiczną aktywnością GnRH, profesor Kochman zainteresował się zsyntetyzowanym we Wrocławiu przez profesora Henryka Kozłowskiego kompleksem Cu-GnRH będącym unikalnym, bo zachowującym strukturę pierwszorzędową, analogiem GnRH. Badania prof. Kochmana wykazały, że po przyłączeniu jonu Cu2+ do pierścienia imidazolowego histydyny (His2) w cząsteczce GnRH, zmienia się konformacja tego dekapeptydu, a kompleks uzyskuje właściwości farmakologiczne i fizjologiczne różniące się od formy natywnej, w tym zdolność do aktywacji szlaku cAMP/PKA w komórkach przysadki.

W końcu lat dziewięćdziesiątych XX w. władze Międzynarodowego Towarzystwa Neuroendokrynologii (International Society of Neuroendocrinology), którego członkiem był profesor Kochman zaproponowały zmianę struktury organizacyjnej Towarzystwa i przekształcenie go w federację krajowych towarzystw neuroendokrynologicznych pod nową nazwą International Federation of Neuroendocrinology (INF). Oznaczało to koniec członkostwa indywidualnego w INS i potrzebę powołania odpowiedniego narodowego towarzystwa neuroendokrynologicznego. Profesor Kochman, wspólnie z jednym z współautorów niniejszego wspomnienia, profesorem Markiem Pawlikowskim, podjęli inicjatywę powołania Polskiego Towarzystwa Neuroendokrynologii (PTNE). Z propozycją zwrócili się do tych badaczy w Polsce, którzy prowadzili badania z zakresu neuroendokrynologii eksperymentalnej i klinicznej. Na apel ten odpowiedziało wówczas 15 osób. Dnia 16 stycznia 2000 r. odbyło się w Łodzi zebranie założycielskie krajowego towarzystwa neuroendokrynologicznego. Profesor Kazimierz Kochman został jego wiceprezesem i funkcję tę sprawował do 2006 roku. W latach 2000-2010 był także pierwszym reprezentantem polskiego Towarzystwa w INF. Występując w tej roli był pomysłodawcą i inicjatorem wprowadzenia do stałej agendy INF-u organizacji letnich szkół dla młodych neuroendokrynologów. Inicjatywa ta spotkała się z wielkim uznaniem środowiska, a pierwsza zorganizowana szkoła letnia była przedsięwzięciem polsko-francuskim, które profesor Kochman współorganizował we Francji w 2006 roku. Idea organizacji szkół letnich jest obecnie kontynuowana przez lokalne towarzystwa neuroendokrynologiczne na całym świecie. W uznaniu swych zasług dla PTNE, profesor Kochman został w 2010 roku wyróżniony tytułem jego członka honorowego.

Jego pozanaukową pasją były historia Polski, sztuka włoska i romantyczna poezja polska. Kochał kwiaty i muzykę Fryderyka Chopina.

Profesor Kazimierz Kochman zmarł w Warszawie 6 listopada 2020 roku. Pozostawił małżonkę Helenę, synów Michała i Andrzeja oraz pięcioro wnuków. Został pochowany na cmentarzu parafialnym w Jabłonnie. Pozostaje w naszej pamięci nie tylko jako wybitny uczony, lecz także człowiek niezwykle skromny i życzliwy.

PROGRAM
VI Zjazd Polskiego Towarzystwa Neuroendokrynologii
Sympozjum satelitarne –V Łódzkie Spotkania Przysadkowe
AULA B, Wydział Biologii i Ochrony Środowiska
Uniwersytet Łódzki
ul. Stefana Banacha 1/3, Łódź

18.11. 2022 (piątek)
Od 10.00 – Rejestracja
11.00 – 12.00 – **Posiedzenie Zarządu Polskiego Towarzystwa Neuroendokrynologii**

Sympozjum satelitarne PTNE

V Łódzkie Spotkania Przysadkowe
Dominujące kierunki terapii gruczolaków przysadki – Agresywne guzy przysadki
12.00 – 14.00
Przewodniczący sesji: prof. dr hab. n. med. Jolanta Kunert-Radek,
dr hab. n. med.Aleksandra Gilis-Januszewska prof. UJ

1. 12.00-12.30 dr hab. n. med. Aleksandra Gilis-Januszewska prof. UJ
Collegium Medicum Uniwersytet Jagielloński
Diagnostyka i leczenie akromegalii o agresywnym przebiegu

2. 12.30-13.00 dr n. med. Maria Stelmachowska-Banaś, prof. dr hab. n. med. Wojciech Zgliczyński
Centrum Medyczne Kształcenia Podyplomowego w Warszawie
Agresywne guzy przysadki

3. 13.00-13.30 prof. dr hab. n. med. Jolanta Kunert-Radek, dr n. med. Natalia Zawada-Kornalewicz
Uniwersytet Medyczny w Łodzi
Analogi somatostatyny II generacji w leczeniu akromegalii

4. 13.30-13.50 prof. dr hab.n.med. Marek Bolanowski
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu
Miejsce analogów somatostatyny I generacji w leczeniu akromegalii
Wykład sponsorowany przez IPSEN

5. 13.50-14.00 Dyskusja

14.00-14.15 Przerwa kawowa

Otwarcie VI Zjazdu Polskiego Towarzystwa Neuroendokrynologii

14.15 – 14.45
Prof. dr hab. Krystyna Pierzchała-Koziec, Przewodnicząca Polskiego Towarzystwa Neuroendokrynologii
Prof. dr hab. Andrzej Kruk, Dziekan Wydziału Biologii i Ochrony Środowiska, Uniwersytet Łódzki
Gość Honorowy: prof. John Russell, The University of Edinburgh, UK,
Pierwszy Prezydent International Neuroendocrine Federation

Wykład inauguracyjny

14.45-15.15 prof. dr hab. n. med. Marek Pawlikowski
Uniwersytet Medyczny w Łodzi
Dwadzieścia lat PTNE na tle rozwoju neuroendokrynologii na świecie

SESJA: Neuroendokrynologia doświadczalna

15.15 – 18.00

Przewodniczący sesji: prof. dr hab. n. med. Marek Pawlikowski, prof. dr hab. Krystyna Pierzchała-Koziec

1. 15.15-15.45 prof. Colin G. Scanes
University of Wisconsin, Milwaukee, USA
Neuroendocrine Functioning in Birds : Novel Findings, Open Questions and Possible Lessons

2. 15.45-16.15 prof. dr hab. n. med. Marta Dziedzicka-Wasylewska
Instytut Farmakologii PAN, Kraków
Badania molekularnych mechanizmów reakcji na stres w modelach zwierzęcych

3. 16.15-16.45 dr. Paula J. Brunton
The University of Edinburgh, UK
Early life programming of the brain & behaviour

4. 16.45-17.15 dr hab. Agata Faron-Górecka
Instytut Farmakologii PAN, Kraków
Hiperprolaktynemia – przyczyna czy skutek leczenia zaburzeń neuropsychiatrycznych

5. 17.15-17.45 dr hab. Marek Wieczorek prof. UŁ
Uniwersytet Łódzki
Zachowanie w chorobie

6. 17.45-18.00 Dyskusja

18.00-18.15 Przerwa kawowa

18.15 – 19.30 **Walne Zgromadzenie PTNE**

19.11. 2022 (sobota)

08.30 – 09.00 Wykład na dobry początek

Przewodnicząca: prof. dr hab. Krystyna Pierzchała-Koziec
8.30-9.00 prof. dr hab. n. med. Katarzyna Winczyk
Uniwersytet Medyczny w Łodzi
Makroformy hormonów – problem diagnostyczno-terapeutyczny

SESJA KLINICZNA I – Choroba Cushinga nadal stanowi wyzwanie

09.00 – 11.00

Przewodniczący sesji: prof. dr hab. n. med. Wojciech Bik,
prof. dr hab. n. med.Bogdan Marek

1. 9.00-9.30 dr hab. n. med. Renata Świątkowska-Stodulska
Gdański Uniwersytet Medyczny

Cykliczny zespół Cushinga

2. 9.30-10.00 prof. dr hab. n. med. Grzegorz Zieliński
Wojskowy Instytut Medyczny
Cewnikowanie zatok skalistych – czy to zabieg bezpieczny?

3. 10.00-10.30 dr hab. n. med. Aleksandra Gilis-Januszewska prof. UJ
Collegium Medicum Uniwersytet Jagielloński
Standardy leczenia w chorobie Cushinga

4. 10.30-10.45 Dyskusja

5. 10.45-11.00 Prezentacje firm sponsorujących

11.00-11.15 Przerwa kawowa

SESJA KLINICZNA II – Interdyscyplinarna

11.15 – 13.30

Przewodniczący sesji: prof. dr hab. n. med. Bogdan Marek,
dr hab. n. med. Dariusz Kajdaniuk

1. 11.15-11.45 dr hab. n. med. Dariusz Kajdaniuk
Śląski Uniwersytet Medyczny w Katowicach
Wazopresyna w uszkodzeniach mózgowia

2. 11.45-12.15 prof. dr hab. n. med. Beata Matyjaszek-Matuszek
Uniwersytet Medyczny w Lublinie
Nowoczesne metody leczenia otyłości

3. 12.15-12.45 dr hab. Agnieszka Baranowska-Bik profesor CMKP
Centrum Medyczne Kształcenia Podyplomowego w Warszawie
Analogi GLP-1 – potencjalne możliwości neuroprotekcyjne

4. 12.45-13.15 prof. dr hab. n. med. Wojciech Bik
Centrum Medyczne Kształcenia Podyplomowego w Warszawie
Covid-19 – czy mężczyźni chorują inaczej?

5. 13.15-13.30 Dyskusja

13.30-13.45 Przerwa kawowa

SESJA POSTEROWA

13.45 – 15.15

Przewodniczący: prof. dr hab. Alina Gajewska,
prof. dr hab. n. med. Katarzyna Winczyk

1. 13.45-14.30 **Neuroendokrynologia doświadczalna**
2. 14.30-15.15 **Neuroendokrynologia kliniczna**

15.15-15.45 – Zakończenie VI Zjazdu PTNE

Oficjalne zakończenie VI Zjazdu PTNE
Podsumowanie firm farmaceutycznych

VI Conference of The Polish Society of Neuroendocrinology
November 18th 2022, Krakow

OPENING CEREMONY

Emeritus Professor **John A. Russell**

Centre for Discovery Brains Sciencies

Medical School University of Edynburgh

j.a.russell@ed.ac.uk

Greetings, and my warm thanks for the invitation to Professor Krystyna Pierzchala-Koziec President of the Polish Society of Neuroendocrinology.

Some of you may remember me from talks I have given previously at Conference of your Society. Actually I have contributed research talks at meeting of your Society across 20 years.

It is disappointing, but understandable in view of the war raging in Ukraine, that we are not able to meet in person. I can though deliver a valedictory message to you.

- This Valedictory Message is to give thanks and best wishes to the many friends and colleagues who have given generous and warm hospitality during my visits to Poland, and my wife Linda whenever she has been able to accompany me.
- I have always felt that being able to travel internationally to present research results among peers and to trainees and to discuss science is a fantastic privilege.
- In parallel, I have also enjoyed this privilege to explore and try to understand the culture of countries I have visited. My Polish colleagues have always shown enthusiasm to educate me and my wife about Poland and its culture…including to enjoy eating dumplings, wild mushrooms and drinking hot chocolate and Chopin!
- A particular purpose of participating in scientific meetings is to seek to establish new collaborations and to refresh collaborations. With my colleagues I have been fortunate to establish successful collaborations with several Polish colleagues. Names in bold in references below.

Short Biography: John A Russell

BSc(Hons), MB ChB, PhD [all University of Edinburgh]

– Academic posts (Lecturer, Senior Lecturer, Reader), Department of Physiology, Medical School, University of Edinburgh

– Personal Chair in Neuroendocrinology, University of Edinburgh. Now Professor Emeritus

Academic positions

– Previously Head (for 5 years), Department of Physiology, Edinburgh University, and Head of Biomedical Sciences (for 3 years).

– Previously Convenor of the Neural Control Systems Interdisciplinary Research Group, Centre for Integrative Physiology, Edinburgh University (for 5 years).

Editorial roles

– Editor-in-Chief (for 12 years, now Emeritus EiC), 'Stress: The International Journal on the Biology of Stress'. Previously Scientific Editor, Journal of Endocrinology,Deputy Editor-in-Chief Journal of Neuroendocrinology

– Formerly Member, Editorial Boards of Frontiers in Neuroendocrinology; Journal of Neuroendocrinology

– Initiated INF Masterclass in Neuroendocrinology Series of edited books: 13 books published since 2015.

Society leaderships

– Past Chairman, British Society for Neuroendocrinology

– Past Secretary, then President, International Neuroendocrine Federation

– Chair, International Neuroendocrine Federation Strategic Action Committee

– Trustee, British Society for Neuroendocrinology.

– Member of numerous International Advisory and Programme Committees for research conferences in neuroendocrinology and stress.

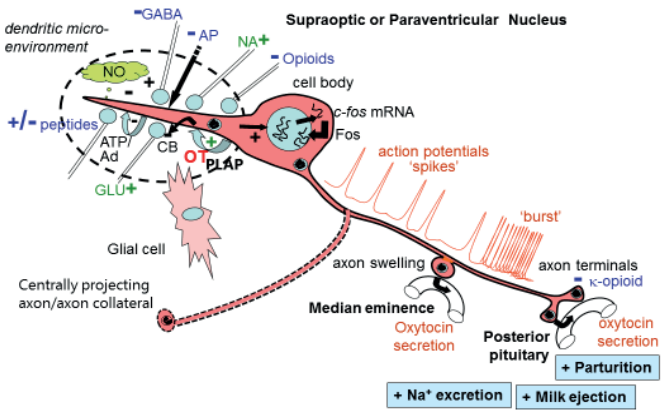
Honours

– Honorary member of Polish Society, of Neuroendocrinology

– Recipient of Ewy Medal (awarded by the University of Agriculture in Krakow)

My research has had two main themes:

1: Oxytocin neuron biology and plasticity, especially in the context of pregnancy



Brunton PJ, Russell JA (2008) The expectant brain: adapting for motherhood. Nat Rev Neurosci. 9(1) 11-25

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2. Reduced neuroendocrine stress responses in pregnancy.

Adrenomedullary responses to stress are attenuated in pregnancy, but more attention has been given to hypothalamo-pituitary-adrenal (HPA) axis changes Douglas AJ, Gooding H, Pierzchala-Koziec K 2007 Attenuated responsiveness of adrenal medulla to stress in pregnancy. Proc Physiol Soc 6 PC 9

Hypothalamo-pituitary-adrenal (HPA Axis)

Our main finding is that HPA axis stress responses in pregnancy are normally attenuated by actions in the brain of the high levels of the neurosteroid allopregnanolone, which activates central opioid inhibition of the HPA axis.

Brunton PJ, McKay AJ, Ochedalski T, Piastowska A, Rebas E, Lachowicz A, Russsell JA. (2009)

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However, this mechanism does NOT prevent adverse fetal programming by maternal social stress! My colleague Dr Paula Brunton will explain this in her talk.

See : Sze Y, Fernandes J, Kolodziejczyk ZM#, Brunton PJ (2022) Maternal glucocorticoids do not directly mediate the effect of maternal social stress on the fetus J Endocrinol Oct 1: JOE-22-0226

MSc Student in Dr Brunton's lab.

Prenatal social stress effects on social memory, behaviours and selective brain gene expression

Pigs

Rutherford KM, Piastowska-Cieseiska A, Donald RD, Robson SK, Ison SH, Jarvis S, Brunton PJ, Russell JA, Lawrence AB. (2014) Prenatal stress produces anxiety prone female offspring and impaired maternal behaviour in the domestic pig. Physiol. Behav. 129: 255-264

The ratio of levels of mRNAs for corticotropin releasing hormone (CRH) receptors 1 to 2 in the amygdala was increased in 10-weeks old female but not male, prenatal social stress (PNS) progeny.

This may explain a neurobiological propensity after PNS for the observed anxiety-related behaviour and disturbed maternal behaviour.

Effects of WAR on human brain prenatal development should be studied. Abnormalities in the brains of those who start WAR should be sought.

Rats

Grundwald NJ#, Benitez DP, Brunton PJ (2016) Sex-dependent effects of prenatal stress on social memory in rats: a role for differential expression of central vasopressin-1a receptors. J Neuroendocrinol. April 28(4

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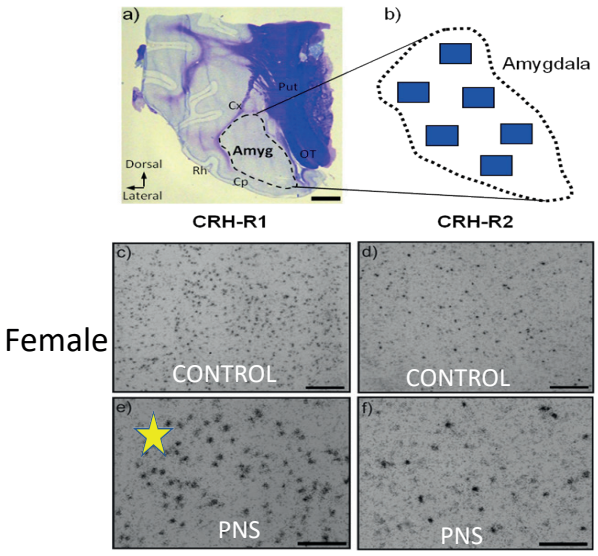
Pig amygdala



FINALLY

I hope that I have encouraged you to see our speciality of Neuroendocrinology as challenging but of great importance to understanding and coping with major human problems.

Our speciality has seen amazing technological advances in the last few decades that can be used to investigate questions about neuroendocrine mechanisms in greater depth and breadth.

Russell JA (2018) Fifty Years of Advances in Neuroendocrinology. Brain Neurosci Adv. 2018 Nov 16;2:2398212818812014. doi:10.1177/2398212818812014. eCollection 2018 Jan-Dec. PMID: 32166160 Free PMC article. Review.

Among possible advances may be understanding impact of contributions from our ancient hominid DNA to neuroendocrine functioning.

I wish you success in your endeavours, and Peace.

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Published: 18 February 2023

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TWENTY YEARS OF PTNE ON THE BACKGROUND OF THE WORLDWIDE DEVELOPMENT OF NEUROENDOCRINOLOGY

Marek Pawlikowski
Medical University of Lodz


Prof. Marek Pawlikowski


Prof. Jolanta Kunert-Radek

Neuroendocrinology is the interdisciplinary domain of biomedical science searching the relation between endocrine and nervous systems. The fundamental discoveries of neuroendocrinology took place in the first part of the 20th century. Let us indicate the pioneers of neuroendocrinology and their main discoveries. Stefan Kopeć (1988-1941), a Polish zoologist (a victim of the second world war, killed in the first great execution of the Polish intelligence in Palmiry near Warsaw) discovered secretory functions of insect brains. Ernest Scharrer (1905-1965) and his wife Berta (1906-1995), discovered secretory phenomena in hypothalamic neurons of several invertebrate and vertebrate animal species including man and founded the term of neurosecretion. Later, W. Bargmann and E,Scharrer demonstrated that the neurosecretory material elaborated in the magnocellular nuclei of the hypothalamus represents vasopressin (antidiuretic hormone) and oxytocin, believed before to be generated in the posterior pituitary lobe and called „posterior pituitary hormones". In fact, these hormones, elaborated in the above mentioned hypothalamic nuclei, are transported to the posterior pituitary through the pituitary stalk. Next, Geoffrey Harris showed that in the hypothalamic control of the anterior pituitary secretion vascular (but not neural) connections play the main role. It was hypothesized that hypothalamic nuclei secrete some humoral factors, called releasing or inhibiting factors, which regulate the pituitary hormone secretion. The intensive research led to their isolation and recognition of their chemical structure. In 1969, two groups directed by Roger Guillemin and Andrew Schally succeeded in recognizing the structure of the thyrotropin releasing factor (hormone) - TRH as piroglutamylo-histydylo-prolinamid. In 1977 this discovery was honoured by Nobel prize in medicine and physiology for R.Guillemin and A.Schally. In the coming years, the atructure of principal hypothalamic neurohormones was established (see Table 1)

Table 1. Discovery of the structure of particular hypothalamic neurohormones .

Neurohormone	Explorers	Data
TRH	A.V. Schally et.al. R.Guillemin et al.	1969
GnRH	A.V. Schally et al. R.Guillemin et al.	1971
SST	P. Brazeau et al.	1973
CRF (CRH)	W.Vale et al.	1981
GHRH	J.Rivier et al.	1982

In Poland, before the final recognition of the GnRH structure by Guillemin's and Schally's groups, Eugeniusz Domanski and Kazimierz Kochman isolated and partially purified GnRH from 5000 ovine hypothalami and indicated several physico-chemical properties of this substance. They also induced the ovulation in sheep using this partially isolated substance. In 1973, the first Polish textbook of neuroendocrinology (Neuroendokrynologia kliniczna, PZWL, Warszawa), written by Rudolf Klimek and Marek Pawlikowski was edited.

In the Scheme 1 (below) I present the successive steps of the investigations on hypothalamic neurohormones.

Scheme 1. Successive steps in hypothalamic neurohormones research
Discovery of biological activity in hypothalamic extracts
Isolation of the active substance
Recognition of the chemical structure
Synthesis
Synthesis of analogs
Studies on animals and in vitro
Clinical studies
New properties
Mechanism of action
Application in diagnostics and therapy

At the end of the 20th century, the International Society of Neuroendocrinology (ISN), the worldwide organization associating the researchers in neuroendocrinology, decided to transform itself into the federation of national societies. Thus, the individual membership was no longer possible and the organization of a national society in Poland became necessary. Two Polish members of ISN, Kazimierz Kochman and Marek Pawlikowski, adressed other Polish scientists active in the field of neuroendocrine research with a proposal of founding the Polish Society of Neuroendocrinology. The initiative was undertaken by 15 persons who, together with K.Kochman and M.Pawlikowski, participated in the founding meeting of the Polish Society of Neuroendocrinology (Polskie Towarzystwo Neuroendokrynologii, PTNE) which take place in Lodz on 26th January 2000. Below there is the list of their names: Alina Gajewska,. Jan Guzek, Marlena Juszczak Michał Karasek, Jan Komorowski, Jolanta Kunert-Radek, Andrzej Lewiński, Stanisława Lipińska,. Jerzy Nowak, Stanisław Okrasa, Franciszek Przekop, Henryk Stępień, Władysław Traczyk, Anna Walczewska, Stefan Zgliczyński. The provisional Committee of PTNE was elected: President – Marek Pawlikowski, vice-president – Kazimierz Kochman; secretary – Jolanta Kunert Radek; treasurer – Marlena Juszczak. PTNE became a member of International Neuroendocrine Federation in November 2001.The first representative of PTNE in INF was Kazimierz Kochman. The first Congress of PTNE took place in Łódź, September, 22th-25th 2002,.The next Congresses debated in Warsaw (October 13th-14th 2006), Cracow (November 25th-26th 2010), Lodz (October 24th-28th 2014), Cracow (September 21th-22th 2018). At the 20th anniversary of the first Congress, it was decided to organize the VI Congress in Lodz, November 18th-19th 2022. The following persons acted as presidents of PTNE: Marek Pawlikowski (2000-2006, since 2010 honorary president), Jolanta Kunert-Radek (2006-2014, since 2014 honorary president), Krystyna Pierzchała- Koziec 2014 until present). A list of the honorary members comprises the following scientists from Poland and abroad, in the alphabetic order: B. Baranowska, A. Bartke, R. Counis, P. Fedor-Freybergh, P. Jaquet , K. Kochman , L. Malendowicz, T. Plant, R. Reiter, J. Russel, J. Sowinski , J. Trouillas, S. Webb, S. Wright , S. Zgliczyński.

Another cyclic event organized by PTNE was the Łódź Pituitary Meeting (Łódzkie Spotkania Przysadkowe). The first one took place in Lodz in 2004. The meetings, organized separately or as satelite symposia of PTNE Congresses, grouped endocrinologists, neurosurgeons, pathologists and radiotherapeutists and played a great role in inducing modern guidelines to pituitary tumors

diagnosis and treatment. Especially, they contributed to the application of immunohistochemistry in diagnosis and pharmacology in treatment of pituitary tumors.

At the end of the 20th century and the beginning of the 21th century, a paradigm of neuroendocrinology was changed. It was clearly shown that neurohormones (neuropeptides) are not produced only by hypothalamic neurons but also by other neurons of central and peripheral nervous systems, diffuse neuroendocrine cells, adrenal medulla, pancreatic islets and, possibly, in other cells. Neurohormones regulate all of the most important vital functions: neural transmission, metabolism, reproduction, endocrine and exocrine secretions and the cell growth. The topic is also enlarged with other problems, not connected directly with neuropeptide hormones, like the role of steroid hormones in the brain differentiation, the role of the pineal gland and melatonin in the regulation of the diurnal and annual rhythmicity, reproduction, immunity, neoplasia and aging. All these problems were studied by the members of PTNE and discussed at the Congresses of this Society.

DIAGNOSIS AND TREATMENT OF AGGRESSIVE COURSE OF ACROMEGALY

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Most pituitary tumors in the course of acromegaly are benign and respond well to multimodal therapy. Nevertheless, some pituitary adenomas may behave in a more aggressive manner, show faster growth, local invasion of surrounding structures, show a high risk of recurrence after surgery, no/or partial response to treatment with 1st generation somatostatin analogues (SSA gen. I) and a worse prognosis.

Patients with an aggressive disease course often require multiple lines of therapy, whose treatment is a clinical challenge and should be carried out by an experienced multidisciplinary pituitary therapeutic team. Recently, intensive research has been carried out on the search for clinical, biochemical, radiological, histopathological and molecular markers of the aggressive course of the disease as well as prognostic factors of response to surgical, pharmacological and radiotherapy treatment.

Young age at diagnosis, male sex, high metabolic activity of the disease determined by both GH and IGF-1 levels, mixed tumors secreting GH and prolactin, AIP, MEN-1 mutations, large tumors with infiltration of cavernous sinuses, hyperintensive in the T2 MRI image (corresponding to a sparsely granulated structure) are prognostic factors associated with a more aggressive course of the disease.

A new, simple and interesting prognostic marker is the paradoxical increase in GH in the glucose inhibition test (defined as> 25% of the baseline value), which according to recent studies involve approximately 30% of patients, usually older ones, with smaller and less invasive pituitary tumors that respond better to treatment with 1st-generation SSA. Among the many histopathological and molecular markers, the most frequently assessed are the histological subtype, the Ki67 index, the expression of type 2 and 5 somatostatin receptors and the expression of the AIP protein. Surgical treatment of aggressive somatotropic tumors is usually not radical, the response to SSA I gene is partial or absent. Adjunctive treatment should include repeated surgery, pharmacological treatment with second-generation SSA (Pasireotide LAR) or GH receptor antagonist (Pegvisomant) available in Poland under the B99 program, and radiotherapy.

Summary: The aggressive course of acromegaly with resistance to conventional treatment may affect approximately 30-40% of patients. When selecting adjuvant therapy, it is necessary to consider risk factors for the aggressive course of the disease and the potential response to treatment with 1st-generation SSA. Modern pharmacotherapy should be implemented without delay, and drug doses should be adjusted until IGF-1 normalization is achieved.

AGGRESSIVE PITUITARY TUMOURS

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An estimated prevalence of pituitary neuroendocrine tumours (PitNET) is 80-100 cases per 100,000. The vast majority of PitNETs are of benign nature and do not metastasize. However, some pituitary tumours may develop a clinically aggressive behaviour, due to increased cell proliferation and invasion in surrounding structures. Aggressive pituitary tumours comprise a very small subset of PitNETs (<5%). An aggressive tumour is best defined by a combination of radiological invasiveness, multiple recurrences, unusual rapid growth rate in spite of optimal use of standard therapies (conventional medical treatments, surgery and radiotherapy). In exceptional cases (0.1-0.2%) aggressive PitNETs can metastasize, which allows for the diagnosis of a pituitary carcinoma.

Histopathological characteristics may indicate a potential aggressiveness. As a first step, determining Ki-67 labeling index is recommended. In patients with Ki-67 labeling index greater than 3%, determining the mitotic count and p53 is advised. A higher Ki-67 is related to aggressiveness but a low Ki-67 index can also occur in aggressive PitNET. Although aggressive pituitary tumours and pituitary carcinomas are rare, they represent an important subject since they cause increased morbidity and mortality and remain challenging to manage. The diagnosis of aggressive pituitary tumours and carcinomas should comprise imaging studies, a full endocrine laboratory evaluation, a neuroophtalmological assessment, histopathological analysis, and in certain cases genetic testing. Follow-up of these tumours needs to be life-long because both acceleration of tumour growth rate and the appearence of metastases may occur many years after the primary diagnosis.

Until recently the therapeutic options were very limited, after repeated surgery and radiotherapy failure. According to the 2018 European Society of Endocrinology (ESE) Clinical Practice Guidelines temozolomide, an oral alkylating agent, should be considered a first-line chemotherapy due to its efficacy and relatively good tolerability. Moreover, a number of new therapies have emerged, improving the survival in various forms of aggressive PitNETs and carcinomas. However, data on their use in aggressive pituitary tumours and carcinomas are still limited to single case reports.

Key words: aggressive pituitary tumour, PitNET, histopathology, chemotherapy, temozolomide

THE SECOND GENERATION SOMATOSTATIN ANALOGUE IN THE TREATMENT OF ACROMEGALY - PROMISING APPLICATION OF PASIREOTIDE IN PATIENTS INADEQUATELY CONTROLLED WITH FIRST GENERATION SOMATOSTATIN ANALOGUES

Jolanta Kunert-Radek, Natalia Zawada-Kornalewicz
Medical University of Lodz

Medical therapy with somatostatin receptor ligands (SRLs) is a standard procedure in the treatment of patients with active acromegaly either after ineffective surgery or as a first line therapy when surgery is contraindicated. Expression of somatostatin receptors 1- 5 (SSTR 1-5) in somatotroph pituitary adenomnas forms the basis for the clinical use of somatostatin analogues (SSA). First generation SSA (octreotide and lanreotide) are generally effective in the treatment of acromegaly, however, about 40% of patients do not achieve control of the disease. This resistance may be explained by overall reduction of SSTR density or differentiated expression of SSTR. First generation SSA bind mainly to SSTR2 and with lower affinity to SSTR5. Comparing to them, second generation somatostatin analogue, pasireotide, has a broader binding spectrum with much higher affinity to SSTR5. Current data demonstrate the superiority of pasireotide over first generation SSA in better biochemical control disease and pituitary tumor shrinkage. Pasireotide LAR tolerability is similar to other SRLs, except for a greater frequency and degree of hyperglycemia and diabetes mellitus. The history of seven patients with uncontrolled acromegaly during therapy with pasireotide is introduced. The patient were previously treated ineffectively with maximum doses of octreotide or lanreotide. Decrease of GH <1 ug/L and IGF-1 normalisation were observed in four patients after 3 months of the therapy with pasireotide 40 mg/28 days. If biochemical control was not achieved pasireotide dose was increased to 60 mg/28days. One patient without any biochemical response was switched off from pasireotide treatment group. Two patients still continue pasireotide therapy with dose 60 mg/28days with normalisation of GH level and with reduction of IGF-1. Pasireotide dose was decreased to 20 mg/28 days in three patients in the last 9–12 months with maintenance of complete biochemical response. In summary, according to our observation pasireotide is a promising therapy option for patients with acromegaly not controlled with first-generation somatostatin analogues. Careful monitoring of glycemic status during therapy as well as appropriate treatment of hyperglycemia are necessary. The reduction of pasierotide dose should be considered in individual patients.

Key words: pasireotide, somatostatin analogues, acromegaly.

THE PLACE OF FIRST GENERATION SOMATOSTATIN ANALOGUES IN THE TERATMENT OF ACROMAGALY

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Somatostatin analogues (SAs or somatostatin receptor ligands) lanreotide and octreotide play a crucial role in medical therapy of acromegaly. They are potent inhibitors of growth hormone (GH) secretion from the pituitary tumour, they are able to reduce tumour size, leading to decrease of insulin like growth factor I (IGF-I) concentration and relief of the clinical symptoms of acromegaly. Hormonal normalization during SAs therapy reduce the occurrence and intensity of acromegaly co-morbidities and complications, finally resulting in the extension of patients' survival. The administration of long-acting formulations of SAs is efficacious, well tolerated and accepted by the patients.

The main indication of first generation SAs is adjuvant therapy, when neurosurgery fails. Some patients are administered SAs as a primary therapy or as a presurgical procedure. In majority cases SAs are given in monotherapy, but combination therapy using first generation SAs together with GH receptor antagonist (pegvisomant) or dopamine agonist (cabergoline) has been reported. The combination of first generation SAs together with second generation SA (pasireotide) is considered in the future medical therapy of acromegaly.

NEUROENDOCRINE FUNCTIONING IN BIRDS: NOVEL FINDINGS, OPEN QUESTIONS AND POSSIBLE LESSONS

Colin G. Scanes
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Following the development of a radioimmunoassay for avian luteinizing hormone (LH) during my Ph. D., it was possible to examine neuroendocrine factors that affected LH release. Based on studies in my laboratory, LH secretion was found to be stimulated by three forms of GnRH but depressed by fasting and protein deficient feeds. Similarly, after we developed an assay for chicken growth hormone (GH), we determined that GH release in chickens was stimulated by both thyrotropin releasing hormone (TRH) and GH releasing hormone (GHRH) and inhibited by somatostatin (SRIF) and triiodothyronine (T3). Moreover, GH release in chickens was increased by feeding a protein deficient diet. Repeated administration of either TRH or GHRH, induced refractoriness to the same but not the different secretagogue. The control of GH release was further examined using ura-2/AM of preloaded cells and an image processing and analysis was performed using an Attoflour system with a Zeiss microscope. Somatotrophs were identified by calcium influx following GHRH challenge followed by immunocytochemistry. They represent about 25 % of anterior pituitary cells. Intracellular calcium was not only increased by GHRH but also TRH, ghrelin, pituitary adenylate-cyclase-activating polypeptide (PACAP), GnRH and leptin. Similarly, leptin and ghrelin evoked increases in intracellular calcium in individual neonatal pig somatotrophs. Only some chicken somatotrophs responded to both GHRH and a sec-

ond secretagogue. For instance, only 21 % of somatotrophs responded to ghrelin while 73 % of somatotrophs responded to TRH. Open questions include the following:

1. Why are there multiple neuropeptides evoking responses in somatotrophs?

2. Why are do only some somatotrophs respond to the different neuropeptides?

In recent studies in collaboration with Professor Pierzchała-Koziec, we have determined that the anterior chicken gastrointestinal tract synthesizes and releases ghrelin with crop expression and release increased by the opioid antagonist, naltrexone. Moreover, these intestinal organs both synthesize and release Met-enkephalin. In additions, both the proventriculus and the duodenum also release both SRIF and insulin-like growth factor-1. The relevance of the multiple neuropeptide in both pituitary and gastrointestinal functioning is discussed.

MOLECULAR MECHANISMS OF STRESS RESILIENCE – STUDIES USING ANIMAL MODELS

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Stress is most often defined as conditions that precipitate a state of equilibrium, and can be about both psychological and physiological balance. Preclinical studies using experimental animals highlight a variety of strategies for coping with stress, reflecting the situation found in the human population. Identifying markers to differentiate these different strategies can be helpful in understanding the mechanisms that regulate the stress response. An interesting animal model exhibiting a stress resilient phenotype is transgenic mice lacking the gene encoding the noradrenergic transporter, NET-KO. Additionally, inter-strain differences in responses to various stress stimuli have been demonstrated between C57Bl/6J and SWR/J mice - the former appeared more passive in their coping strategy, while the latter exhibited a more active strategy. Also rats subjected to chronic mild stress can be divided into stress-susceptible and stress-resilient group. One of recently appreciated levels which might help to identify differences between these groups is the level of micro-RNAs (miRNAs) in the peripheral blood (serum) and selected brain regions of the experimental animals. MiRNAs are short RNA sequences that are involved in the regulation of protein-coding transcripts. There are far fewer of them (about 2,000) than genes (e.g., 20,000-30,000) or transcripts - so by profiling miRNAs in screening, important proteins or signaling pathways can be more easily identified. Often a multidirectional research approach is used, from behavioral studies through advanced microRNA level assays and in vitro experiments to complex bioinformatics analyses, which allows to identify target sequences for selected miRNAs (whose expression was important in the reactivity of experimental animals to stress stimuli) and verify the results at the biochemical level in the form of expression measurements of selected genes and also verify the signaling pathways activated by these sequences. Intracerebral administration of selected miRNA sequences might be useful to reverse the phenotype from susceptible to resilient to stress and vice versa.

PRENATAL PROGRAMMING OF THE BRAIN AND BEHAVIOUR – WHAT ARE THE MECHANISMS?

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Prenatal stress (PNS) can program long-lasting neuroendocrine and behavioural changes in the offspring. Often this programming is maladaptive and sex-specific. For example, adult PNS male, but not PNS female offspring, display increased anxiety-like behaviour; whereas both sexes show enhanced hypothalamo-pituitary-adrenal (HPA) axis responses to stress. Direct transfer of maternal glucocorticoids to the fetuses is often considered to mediate the programming effects of maternal stress on the offspring. However, protective mechanisms including hyporesponsiveness of the maternal HPA axis and placental 11β-hydroxysteroid dehydrogenase-2 (11βHSD2), which inactivates glucocorticoids, limit mother-to-fetus glucocorticoid transfer during pregnancy. Moreover, a clear relationship between maternal stress, maternal & fetal glucocorticoid concentrations has not been convincingly demonstrated. Therefore, we aimed to investigate the signal that permits maternal psychosocial stress to be transmitted to the fetus and whether fetal programming effects can be prevented or reversed.

Using a social stress model in pregnant rats, we found that while corticosterone secretion was significantly greater in stressed dams compared with controls, there was little impact on circulating corticosterone concentrations in the fetus and no change in the fetal brain. In addition, the 11βHSD2 placental barrier appeared intact, minimising glucocorticoid transfer across the maternal-fetal interface. Nevertheless, oxidative stress evidently does play a role in fetal programming. Social stress increased oxidative stress markers in the mother, placenta and fetus; and maternal antioxidant treatment during pregnancy prevented some of the adverse effects of prenatal stress on the offspring's brain and behaviour.

In conclusion, maternal glucocorticoids do not appear to be directly involved in mediating the programming effects of maternal social stress on the fetus, but may act in an indirect, and sex-dependent manner to induce oxidative stress.

Support: Biotechnology and Biological Sciences Research Council; British Society for Neuroendocrinology

HYPERPROLACTINEMIA - CAUSE OR EFFECT OF TREATMENT OF NEUROPSYCHIATRIC DISORDERS

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The effects of prolactin (PRL) on the nervous system induce wide range of changes in the female brain during pregnancy and it contributes to inhibition of the hypothalamic-pituitary axis. All these changes are necessary for the behavioral and physiological adaptations of the young mother to enable reproductive success. PRL-driven brain adaptations are also important for regulating maternal emotionality and well-being. While hyperprolactinemia (elevated PRL levels) is a natural and beneficial phenomenon during pregnancy and lactation, in other situations it is

often associated with serious endocrine disorders. PRL is known as the stress hormone, so it appears that its impaired secretion of this hormone may be an important factor in the development of neuropsychiatric diseases, for which stress is an important trigger. In animal models of depression, basal PRL levels have been shown to correlate with response to treatment with antidepressants. PRL has also been shown to affect levels of the blood-brain barrier (BBB)-specific proteins (Tight junction and adherent proteins). The alteration of BBB permeability is crucial for the proper work of drugs. Thus, it seems that PRL may be an interesting biomarker of response to treatment with antidepressants.

SICKNESS BEHAVIOR - WHAT WE ARE KNOW

Marek Wieczorek
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The seminal observations, published by Besedovsky and his team in the 80's of the XX century, indicated that intraperitoneal administration of interleukin-1 to the experimental animals activated the hypothalamo-pituitary-adrenal axis (HPA) elevating circulating plasma concentrations of ACTH and corticosterone.

Based on the above, precise understanding of the mechanisms of reciprocal relationship of the nervous and the immune systems has been the subject of numerous studies for recent years in many laboratories throughout the world. This specific function of the mechanisms of communication between the immune and the central nervous system have the essential meaning, especially in the situation when the organism starts the fight against bacterial or viral infections. Detailed understanding of the mechanisms of these influences has also essential meaning from the medical point of view. It may be helpful in development of the new methods of treatment of many infection diseases and may provide better methods to neutralize possible side effects of the therapy.

The next experiments performed by many authors indicated that in response to infection and inflammation we can observe decreases in food intake, and locomotor activity, and general depression of mood. On the other hand, it is known that a positive mental attitude favors the healing process. Based on this, the physiological and pathophysiological processes underling the behavioral and neural mechanisms connected with sickness behavior will be discuss.

Key words: sickness behavior, HPA axis, infections, inflammation

HORMONE MACROFORMS – A DIAGNOSTIC AND THERAPEUTIC PROBLEM

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Hormone macroforms are the large complexes usually composed of a monomeric molecule of hormone and immunoglobulin. In clinical practice, macroprolactin (macro-PRL) is the macroform most commonly detected in the human blood, however, the literature data show the occurrence of macromolecules of other pituitary hormones, mainly thyrotropin, and less often gonadotropins (LH, FSH).

The main diagnostic problem is that macroforms have a very little or no biological activity compared to a single hormone molecule, while maintain immunoreactivity in the laboratory tests. A large amount of macroforms in the blood can cause an increase of hormone concentration above the upper reference value, but without the typical clinical symptoms of an excess of the hormone in the patient.

In these cases, in order to avoid diagnostic errors and inappropriate therapeutic decisions, testing for macroforms should be performed. The best, but time-consuming and costly method for detection macroforms is chromatography. In scientific research, the ultrafiltration method is also used to detect the high-molecular complex of hormone. However, in laboratory practice (nowadays targeting only macro-PRL), the precipitation with polyethylene glycol is mainly used.

The lecture will present the current literature data on macroforms of various hormones and discuss the most common macroforms – macro-PRL and macro-TSH, as well as techniques for their detection and the clinical interpretation of laboratory results.

Key words: hormone macroforms, macroprolactin, macrothyrotropin, precipitation with polyethylene glycol

CYCLIC CUSHING'S SYNDROME

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Cyclic Cushing's syndrome is a disease characterized by transient hypercortisolemia shifting into normocortisolemia. Three periods of hypercortisolemia interspersed by two phases of normocortisolemia confirm the diagnosis. Evaluation of periodic hypercortisolemia is one of the greatest struggles in modern endocrinology due to unpredictable duration and frequency of phases, diverse clinical presentation, and various etiologies of the disease.

As the hypersecretion of cortisol is transient, only limited signs and symptoms, including hypokalemia, cardiac arrhythmias, or peripheral edema, might develop. In most cases, the disorder is suspected in individuals presenting features typical for hypercortisolemia who do not meet full hormonal criteria of Cushing's syndrome. Periodic hypercortisolemia should also be considered in patients with confirmed autonomous overproduction of cortisol who became normocortisolemic over the period of observation. Final diagnosis of cyclic Cushing's syndrome often requires multiple rounds of diagnostic tests. The chance of accurate diagnosis is the highest during an active phase of the disease or shortly after it concludes.

Differential diagnostics of intermittent hypercortisolemia should include use of exogenous glucocorticoids, mild autonomous cortisol secretion (previously known as subclinical Cushing's syndrome), non-neoplastic hypercortisolemia (previously: pseudo-Cushing's syndrome), resistance to glucocorticoids, and drug interferences.

STANDARDS OF TREATMENT IN CUSHING'S DISEASE

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Cushing's disease (CD) is a rare and serious disease associated with increased mortality and a deterioration in quality of life. In the past, the median survival of patients with CD was less than 5 years. Effective treatment reduces mortality, improves the course of comorbidities and improves long-term quality of life.

Despite advances in knowledge, treatment of CD remains a clinical challenge. The main goals of CD treatment are normalization of cortisol secretion, control of pituitary tumor size, reduction of clinical symptoms and comorbidities, improvement of quality of life and reduction of mortality.

In 2019, new recommendations for the diagnosis and treatment of CD prepared by the Pituitary Society were published, which emphasize the need to individualize treatment depending on the severity of the disease, accompanying comorbidities, possible side effects, individual patient preferences and local drug availability.

Transsphenoidal pituitary tumor resection remains the treatment of choice, but approximately one-third of patients undergoing initial surgery may require second- and/or third-line treatments such as reoperation, radiotherapy, conservative therapy, or bilateral adrenalectomy. Pharmacological treatment is used in cases of persistent or recurrent hypercortisolemia, in patients who are ineligible or refuse to undergo surgery, as a bridge therapy during radiotherapy, and as a pre-surgery therapy in severe hypercortisolemia.

Currently, the pharmacological treatment includes steroidogenesis inhibitors (osilodrostat, metopyrron, levoketoconazole, ketoconazole), a short- and long-acting second generation somatostatin analogue (Pasireotide and Pasireotide LAR), a dopaminergic receptor agonist (cabergoline) and an inhibitor of the glucocorticoid receptor (Mifeprtiston, available in the USA). In critically ill patients who require parenteral therapy, etomidate may be the drug of choice. In some cases, combination therapy should be considered, which is associated with improved control of treatment compared to monotherapy (especially when drugs from different groups are combined) and reduction of side effects by using lower doses of drugs.

VASOPRESSIN IN BRAIN INJURIES

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Abnormalities of salt and water balance are common in patients with brain injuries. In neurosurgical centers, most of the endocrine consultations deal with this problem. The water homeostasis is disturbed as a result of the underlying disease, but also as a result of neurosurgical intervention and postoperative treatment. The most common electrolyte disturbance is hyponatremia, which occurs in 10-50% of the patients. Hyponatremia in brain injuries occurs in connection with subarachnoid hemorrhage (SAH), brain tumors, traumatic brain injury (TBI), and after pituitary surgery. Neurosurgical patients are more prone than others to develop symptoms of hyponatremia due to additional damage to the CNS structures – the influence of the primary disease process on the surrounding tissues, increased intracranial pressure, neurosurgical intervention, and critically ill patients also due to hypoxemia, hypercapnia, and acidosis. Interestingly, some of the damage associated with hyponatremia may already appear at slightly higher natremia values compared to other situations. Hyponatremia in brain injuries arises in three pathomechanisms – Syndrome of Inappropriate Antidiuretic Hormone (SIADH), Cerebral Salt Wasting Syndrome, and secondary adrenal insufficiency. Hyponatremia is an unfavorable prognostic factor, it prolongs hospitalization, although it does not necessarily increase mortality. Central Diabetes Insipidus (CDI) and the associated excess water loss, in the acute phase of neurosurgical intervention, is also common, is usually transient, and if patients have an efficient sensation of thirst, they do not develop dehydration and subsequent hypernatremia. CDI appears in association with pituitary surgery, pituitary apoplexy, TBI, SAH, intracerebral hemorrhage, subdural hematoma, and brain abscess. 3-5% of patients with CDI develop a three-phase reaction – transient CDI, followed by SIADH (up to about 2 weeks) and finally persistent CDI. Adipsic CDI occurs when the osmoreceptors in the anterior hypothalamus are damaged, resulting in no sensation of thirst and no ADH secretion in response to an osmotic stimulus, despite retaining the ability to synthesize and release ADH in response to a non-osmotic stimulus, such as hypotension. Careful correction of both hyponatremia and hypernatremia is required, and the complications of too rapid correction of hyponatremia are usually irreversible.

GLP-1 ANALOGS - POTENTIAL NEUROPROTECTIVE ACTIVITIES

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There are reports that GLP-1 under physiological conditions affect neuronal functions such as thermogenesis, blood pressure control, neurogenesis, neurodegeneration, retinal repair, and CNS energy homeostasis. GLP-1 is also involved in reducing oxidative stress, regulating autophagy, and modulating central nervous system (CNS) pathways along with protective functions and anti-inflammatory activation. The studies showed the expression of GLP-1 mRNA in the cerebral cortex, hippocampus, thalamus, and hypothalamus.

A question may be raised whether GLP-1 analogs also have neuroprotective activity. Will they be used as preventers of neurodegenerative diseases?

The available studies indicate that GLP-1 analogs in diabetes have also a positive effect on β-amyloid peptide aggregation in Alzheimer's disease (AD) and dopamine (DA) activity in Parkinson's disease (PD). GLP-1RA has a beneficial effect on the course of cerebral ischemia in animal models. GLP-1 analogs may also influence cognitive impairment induced by diabetes and/or obesity, improving learning and memory by modulating synaptic plasticity and reducing hippocampal neurodegeneration.

Additionally, several other mechanisms to ensure neuroprotection should be considered. Activation of GLP-1R enables anti-

oxidant activity in the CNS, resulting in the inhibition of oxidative stress-induced apoptosis of hippocampal neurons and reduced damage to neuronal networks. GLP-1 analogs decrease neuroinflammation in neuronal structures and improve glial morphology and neurite complexity by inhibiting TNF-α mediated inflammation. Not without significance is the effect on insulin signaling pathways. Patients with decreased levels/activity of insulin in the CNS are more prone to AD, PD, hippocampal atrophy, attention disorders as well as neurodegenerative disorders, and in this group, the use of GLP-1 analogs may reduce impaired glucose utilization in the CNS and affect brain insulin deregulation. GLP-1 analogs cross the blood-brain barrier and can directly affect neuronal apoptosis. They can also suppress pathophysiological pathways that stimulate apoptosis, such as oxidative stress and inflammation.

Other beneficial neuroprotective mechanisms include reduction of neurotoxicity (e.g. glucotoxicity), effects on neurogenesis and synaptic plasticity, and direct central effects.

GLP-1 analogs seem to be a potential drug that could find application in neuroprotection.

Key words: GLP-1, GLP-1 analog, neuroprotection, insulin, oxidative stress

COVID-19 - DO MEN HAVE A DIFFERENT COURSE THAN WOMEN?

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Covid 19 infection is a significant medical problem, not only due to pulmonary or cardiological complications but also its effect on the endocrine system. This effect applies not only to disturbed functioning of the hypothalamic-pituitary-thyroid axis in the form of euthyroid sick syndrome or an increased risk of sub-acute thyroiditis. Transient disorders of the pituitary gland, adrenal glands, or gonads may be a significant problem as well. The negative influence of the virus is related to the presence of ACE2 and TMPRSS2 receptors in the cells of the endocrine organs. It should also be highlighted that obesity, type 2 diabetes, and cardiovascular diseases, are related to a more severe course of infection.

Epidemiological studies have also shown that the Covid 19 infection course in men may be more severe than in women, and is associated with multiple times greater risk of intensive care unit admission and, consequently, a greater risk of death.

Therefore, how can gender influence the course of Covid 19 infection? Numerous studies indicate a different immune response in men and women. These differences are genetically determined, resulting in a stronger antiviral response in women. The level of pro-inflammatory cytokines in men is also higher than in women. The beneficial effect of estrogens and the immunosuppressive effect of testosterone have also been postulated. Environmental factors related to more frequent compliance with sanitary recommendations by women are not without significance.

To summarize, the potentially more severe course of Covid 19 infection in men is multifactorial. However, the differences in immune response in men and women seem to be of significant importance.

Key words: Covid 19, immune system, endocrine system, gender differences

MODERN METHODS OF OBESITY TREATMENT

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Obesity is a chronic disease characterized by overaccumulation of adipose tissue. The large number of obesity-related complications, estimated at 200, make obesity a significant health problem both on an individual and social scale. The problem of obesity prevalence has increased since the COVID-19 pandemic due to epidemiological restrictions.

The pathogenesis of obesity is complex and multifactorial. In its pathogenesis participate peripheral mechanisms, such as gastrointestinal neurohormones: PP, PYY, GLP-1, OXM, ghrelin, and adipocytokines, chiefly leptin, and many others. Peripheral stimuli are integrated in the hypothalamic centers: the appetite center and the satiety center. In the hypothalamic system, which plays a major role in the regulation of food intake, the information inflow from the digestive tract and adipose tissue is processed. The POMC and CART systems, as well as the NPY and AgRP systems play a key role in the hypothalamic regulation of appetite.

The treatment of obesity is absolutely indispensable. We have both pharmacological and surgical methods of obesity treatment. The guidelines of scientific societies specify the indications for commencing obesity treatment. In the case of pharmacotherapy, it is BMI > 30 kg/m^2 or BMI > 27 kg/m^2 with ≥ 1 complication typical for excess body fat. The drugs approved for the treatment of obesity are GLP-1 analogues: liraglutide and semaglutide (the latter currently unavailable in Poland in the above indication), a combined preparation of bupropion and naltrexone, and orlistat. The effectiveness of pharmacotherapy in reducing body weight is estimated at 8–15% in relation to the initial body weight, and in the case of semaglutide, even up to 20%. Thus, the effectiveness of pharmacotherapy ranks this method between behavioral treatment and bariatric surgery. Currently, numerous new drugs that aid weight reduction are either already introduced to the market, or at an highly advanced stages of clinical trials. These modern drugs include the MC4 melanocortin receptor agonist setmelanotide, and the GLP-1 and GIP dual agonist – tirzepatide.

In conclusion, obesity as a chronic and irreversible disease, without a tendency for spontaneous remission, and therefore requires treatment, which should be initiated as soon as possible after making diagnosis. The goal of obesity treatment is not only to reduce body weight, but also – especially in the long term – to prevent possible complications of obesity.

POSTERS SESSION

THE EFFECTS OF OPIOID RECEPTOR BLOCKADE ON NATURAL KILLER CELL CYTOTOXICITY, CYTOKINE AND NEUROENDOCRINE RESPONSES DURING ACUTE RESTRAINT AND ACUTE EXERCISE IN PIGS

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Background The experimental data strongly indicate that various types of stressors, including physical exercise (EX) and immobilisation (IMO), can influence immune function. The mech-

anisms underlying the immunostimulatory effect in particular, are still unclear and appear to be mediated through the opioid system.

Purpose This study evaluated porcine natural killer cell cytotoxicity (NKCC), plasma cytokines: interleukin (IL) 1β, IL-6, IL-10, IL-12 and tumor necrosis factor-α and plasma stress-related hormones: prolactin (PRL), growth hormone, β-endorphin (BEND), ACTH and cortisol (COR) during a 20 min restraint (IMO) or 20 min exercise (EX) after saline or naloxone (NX, 1mg/kg BW) administration.

Methodology The experiments were performed on 36 catheterised pigs of polish 990 line, divided into 6 groups, subjected IMO or EX twice or a mix of both IMO and EX (IMO+EX and EX+IMO), with one hour of rest between stressors. NKCC was determined by 51Cr-release assay against K-562 target cells, plasma concentrations of cytokines and hormones were analysed using ELISA or RIA.

Results It was shown that administration of NX prior to IMO diminished IMO-induced suppression of NKCC, while administration of NX prior to EX potentiated the immunostimulatory effects (both effects $P<0.05$ compared with control groups). In the mixed groups, the effect of naloxone administration depended on the order in which the loads were applied: in IMO+EX group attenuation of the immunosuppressive effect was observed, whereas in the EX+RS group, only immunostimulatory effects were observed. Moreover, these changes correlated positively with PRL, BEND and IL-10 concentrations, whereas they correlated negatively with COR, IL-1 and IL-6 concentrations.

Conclusion Our results suggest that the type of stressor may be important for both the magnitude and direction of immunomodulatory changes and the involvement of the opioid system could also depend on the type and sequence of the stressor applied.

Key words: pig, stress, natural immunity, opioid, cytokines, exercise

DIABETES: THE LINK BETWEEN OXIDATIVE STRESS AND INFLAMMATION - THE POTENTIALLY PROTECTIVE EFFECT OF SEA BUCKTHORN

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Background Sea buckthorn (*Hippophae rhamnoides* L.) is widely used in the world as a herbal medicine and food additive. The unique properties of sea buckthorn are evidenced by the presence of both lipophilic antioxidants (mainly carotenoids and tocopherols) and hydrophilic antioxidants (flavonoids, tannins, phenolic acids, ascorbic acid) in extremely large amounts. Stress is part and parcel of the life of all animals. It is defined as the sum of biological responses to any adverse stimulus, physical, mental or emotional, external or internal, that tends to interfere with homeostasis. Oxidative stress, which is a consequence of an imbalance between oxidants/antioxidants, is, according to one theory, the result of metabolic disturbances occurring in the course of diabetes. Another theory is that oxidative stress underlies the pathogenesis of diabetes. Hence, analysis of the activity of enzymes with antioxidant properties can provide information about possible strategies for the prevention and/or treatment of diabetes. Due to its rich composition and properties, sea buckthorn is the subject of numerous studies, including the use of its extract as a substance supporting the treatment of diabetes.

Purpose The aim of the study was to investigate the relationship between the level of corticosterone and other markers of stress and inflammation after sea buckthorn extract administration in Zucker diabetic fatty rats.

Results The study found no correlation between serum corticosterone levels and other stress response markers such as catecholamine excretion. On the other hand there was a significant correlation between serum corticosterone levels and some markers of inflammatory response such as white blood cell counts.

Conclusion The current study found that sea buckthorn extract has potential antioxidant, anti-inflammatory and antidiabetic effects, suggesting it could be developed into a new nutraceutical or natural drug and as a protective effect on the body, protecting it from stress.

Key words: Sea buckthorn, stress, antioxidants, anti-inflammatory effect, diabetes

MET-ENKEPHALIN AND GHRELIN CHANGES IN THE BRAIN - GASTROINTESTINAL AXIS IN NEWLY HATCHED CHICKENS

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Background The growth and development of the brain-gastrointestinal (GI) axis are under the control of the nervous and endocrine systems. Met-enkephalin, and ghrelin, neuropeptides, stimulate food intake and growth at the central and peripheral levels. Both neurohormones are involved in the regulation of energy homeostasis, particularly during development. In spite of many experiments, their role in the regulation of the brain-gastrointestinal axis activity is still sparse and needs a specific animal model for research.

Purpose The aim of the study was to investigate the changes in the synthesis and concentrations of Met-enkephalin and ghrelin in the several structures of brain and GI segments of newly hatched chickens, an unique animal model.

Methodology The experiment was carried out on chickens, 2 hours after hatching (day 0) and 24 hours after hatching (day 1). Met-enkephalin and ghrelin gene expression (mRNAs of PENK and GHRL) and both neurohormones concentration were measured by RT-PCR and RIA methods, respectively.

Results The expressions of mRNAs of PENK and GHRL on day 1 were decreased in the hypothalamus and increased in the pituitary. The concentration of both peptides was higher in both tested brain structures 24 hours after hatching. On day 1 significant increases of PENK mRNA expression were observed in the crop and stomach. In contrast, GHRL mRNA expression was decreased in the stomach and duodenum. On the other hand, 24 hrs after hatching, the highest concentration of Met-enkephalin was seen in the duodenum; in case of ghrelin, a significant concentration increase was noticed in the crop.

Conclusion The obtained results suggest that Met-enkephalin and ghrelin are important neurohormones modulating the growth and development of the brain-gastrointestinal axis in the chicken model.

Key words: Met-enkephalin, ghrelin, chickens, brain-gastrointestinal axis

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THE ALL-TRANS-RETINOIC ACID TREATMENT INCREASES ADIPONECTIN SYNTHESIS AND SECRETION BY PERIVASCULAR ADIPOSE TISSUE IN ATHEROSCLEROSIS

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Background All-trans-retinoic acid (atRA) is an active metabolite of vitamin A that plays a potential role in the prevention of cardiovascular diseases. The perivascular adipose tissue (PVAT) is located outside of the blood vessel with direct contact with the adventitial layer. PVAT secrets several adipokines playing an important role in vascular function. Adiponectin is an endogenous hormone, which exerts vasculoprotective and anti-inflammatory effects. It has been shown that adiponectin limits the initiation of atherosclerotic plaque formation.

Purpose In the current study, we investigated the atRA influence on atherosclerosis and adiponectin synthesis in PVAT.

Methodology Experiments were performed in 8 weeks male mice: Apo-E (model Aof atherosclerosis) and C57BL/6J treated with vehicle (corn oil) or atRA for 8 weeks. AtRA or vehicle was administrated by a stomach tube. All animals were fed on a normal diet. We performed the Oil Red O staining for the measurement of atherosclerotic lesions in the aortic root. Furthermore, adiponectin mRNA level and adiponectin concentration were measured in PVAT.

Results The mean atherosclerotic lesion area in the aortic sinus of the atRA group was 53% lower than in the vehicle-treated Apo-E mice ($p<0.001$). Adiponectin mRNA level and adiponectin concentration were significantly increased in PVAT of the Apo-E group treated with atRA when compared to the vehicle-treated group of Apo-E mice ($p<0.05$).

Conclusion The present study suggests that atRA increases adiponectin synthesis and secretion by PVAT and may ameliorate atherosclerosis in Apo-E mice.

Key words: adiponectin, perivascular adipose tissue, Apo-E mice, atherosclerosis

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CENTRAL MECHANISMS OF COMPENSATION A LONG-TERM IMPAIRMENT OF IMMUNOSENSORIC AND IMMUNOSUPPRESIVE FUNCTIONS OF VAGUS NERVE

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Background Disturbance of vagal activity is observed in many neurodegenerative and mental diseases involving inflammation. Vagus nerve is one of the main routes of neuroimmune-communication and plays an essential role in generating the central response to peripheral inflammation. Literature data suggest that effects of vagotomy vary over time and that the initial severity of pro-inflammatory effects subsides with the prolonged recovery period after the procedure.

Purpose Performed study investigated possible alterations in rat central neurochemistry, behavior and biochemistry which could evidence existing of natural compensation of disturbed vagal immunesensory and immunosuppressive functions

Methodology The research was carried out on Wistar rats. A behavioral elevated plus maze test was performed and various biochemical and molecular analysis techniques such as HPLC, RIA, ELISA, RNA microarrays and RT-qPCR were used.

Results Thirty days after subdiaphragmatic vagotomy, the functioning of the serotonergic and dopaminergic systems was altered in relation to sham animals. These changes are partially mitigated at the early stages of intraperitoneal inflammation, possibly through the interaction of alternative neuroimmunecommunication mechanisms (COX /PGE2) with the Vagus Afferent Network. Despite the observed neurotransmission changes, one month after surgery, secretory activity of the HPA axis was similar to sham-operated animals, probably due to the compensatory inhibitory activity of the amygdala. The locomotor activity of vagotomized animals was reduced, regardless of the inflammation. The analysis of the striatal neurotransmission activity suggests that subdiaphragmatic vagotomy may lead to decreased interest in social contacts during peripherally developing inflammation. Moreover, the subdiaphragmatic vagotomy may intensify the pain sensations by disrupting the peripheral secretion of endogenous analgesic substances.

Conclusion Obtained data constitute the basis for more detailed studies on the relationship between persistently impaired vagal activity and mental disorders related to social withdrawal, and neurodegenerative diseases related to disturbance of the neurotransmission activity of the central nervous system.

Key words: subdiaphragmatic vagotomy, intraperitoneal inflammation, sickness behavior, monoamines, hypothalamus, striatum

THE ROLE OF LEPTIN AND ADIPONECTIN DISTURBED IN PERITUMORAL ADIPOSE TISSUE IN THE REGULATION OF EXPRESSION OF RENAL CANCER-ASSOCIATED MICRORNAS.

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Background Obesity is among the main epidemiological factors associated with the development of renal cell cancer (RCC). A special role in cancerogenesis is assigned to adipokines (mainly leptin and adiponectin) secreted by adipose tissue (AT). Currently, little is known about adipokines' expression in peritumoral AT and their paracrine effects on RCC cells. Moreover, there is no research regarding the regulation of microRNAs by adipokines in RCC.

Purpose We aimed to: i) analyze the level of leptin and adiponectin in AT tissue located in direct proximity to RCC tumor

(RATT) or distant from the tumor (RATN) as well as in the conditioned media (CM) from their *ex vivo* culture (CM-RATT and CM-RATN); ii) examine their role in the regulation of expression of cancer-associated microRNAs.

Methodology The expression of adiponectin and leptin was analyzed by qPCR in RATT and RATN as well as using cytokines arrays in CM-RATT and CM-RATN samples. RCC-derived cells were treated with 500 ng/ml of leptin or 10 µg/ml of adiponectin for 48h, then the expression of microRNAs and their target genes was analyzed using qPCR.

Results The expression of adiponectin was downregulated in RATT, while this tissue secretes higher amounts of leptin. Treatment of RCC-derived cell lines with leptin or adiponectin affects the expression of microRNAs. Specifically, miR-21-5p, miR-182-5p and miR-199a-5p were upregulated, while miR-27b-5p was downregulated in cells treated with leptin. Adiponectin stimulated expression of miR-21-5p while inhibiting expression of miR-27b-5p and miR-199a-5p. Leptin decreased, while adiponectin increased expression of DDR1, previously reported as miR-199a-5p target gene.

Conclusions These results suggest disturbed expression of adiponectin and leptin in peritumoral adipose tissue and its secretome. Moreover, we have shown novel adipokine/leptin-miR-199a-DDR1 axis in RCC, possibly contributing to cancer progression.

Key words: adipose tissue, adiponectin, leptin, obesity, ccRCC, microRNA

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NICOTINIC ACID PROTECTS THE DIFFERENTIATED SH-SYSY CELLS AGAINST AMYLOID β TOXICITY

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Background Alzheimer's disease (AD) is a kind of neurodegenerative disease. The major pathological hallmarks of AD are amyloid β (Aβ) plaques and neurofibrillary tangles along with loss of neurons and synapses in the brain. The current direction of research is focused on identifying factors that can protect neurons against Aβ toxicity. Niacin may be relevant for AD because niacin mediates energy metabolism, mitochondrial functions, calcium homeostasis, and survival and cell death.

Purpose We aimed to assess the effect of nicotinic acid (NA) on Aβ1-42 –induced cytotoxicity in differentiated SH-SY5Y cells.

Methodology The SH-SY5Y cells were differentiated for 10 days. Next, the cells after 1h preincubation with NA [10nM] were incubated for another 24h with Aβ [5µM]. MTT and LDH assays were used to assess viability and cytotoxicity, respectively. The expression of synaptic markers was measured by RT-qPCR and immunocytofluorescence methods.

Results Aβ1-42 treatment significantly decreased the viability of the SH-SY5Y cells and increased the release of LDH from the SH-SY5Y cells ($p < 0.001$). The NA pre-treatment increased the cell viability ($p < 0.001$) and decreased the release of LDH ($p < 0.05$). Aβ1-42 administration significantly decreased mRNA levels of synaptophysin ($p < 0.001$) and decreased relative TUJ-1 fluorescence intensity ($p < 0.01$). The NA pre-treatment reversed the effect of Aβ1-42 on expression of synaptophysin ($p < 0.05$) and TUJ-1 ($p < 0.05$).

Conclusion Niacin abolished the neurotoxic effects of Aβ1-42 on differentiated SH-SY5Y cells.

Key words: Alzheimer's disease, neurodegeneration, niacin

This study was supported by CMKP grants No 501-1-31-22-21 and 501-1-31-22-22.

EFFECT OF KYNURENIC ACID ON GENE EXPRESSION AND REPAIR ACTIVITY OF SELECTED DNA GLYCOSYLASES IN THE HIPPOCAMPAL CA1 FIELD IN SHEEP

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Background Oxidative DNA damage is one of common causes of many neurodegenerative diseases. Recently, the importance of kynurenic acid (KYNA), an active metabolite of tryptophan, has increased as a neuroprotective molecule in the brain. Therefore, we investigated the central effects of KYNA on mRNA expression of selected base excision repair (BER) pathway enzymes and their excision efficiency of damaged nucleobases in the hippocampal CA1 field in sheep.

Methods The anestrous sheep (n=18) were surgically implanted with a stainless steel guide cannula into the third brain ventricle and after recovery infused with: 1) Ringer-Locke solution (RLs, control); 2) the lower (4×5 µg/60 µL/30 min) or 3) the higher (4×25 µg/60 µL/30 min) KYNA doses. The treatment was performed in a series of four 30 min infusions, at 30 min intervals, from 10:00 to 14:00. Immediately after the experiment, sheep were slaughtered and the hippocampal CA1 field was dissected from the right hemisphere of the brain. mRNA expression of selected BER pathway enzymes: 8-Oxoguanine glycosylase (OGG1), N-Methylpurine DNA glycosylase (MPG) and thymine DNA glycosylase (TDG) and their repair activity were determined by Real Time-PCR and biochemical methods, respectively.

Results The lower KYNA dose increased mRNA expression ($P<0.01$–$P<0.001$) for all glycosylases and also the excision efficiency of 1,N6-ethenodeoxyadenosine (εA, $P<0.001$) and 3,N4-etheno-deoxycytosine (εC, $P<0.001$) compared to controls. The higher KYNA dose increased mRNA abundance for OGG1 ($P<0.001$) and MPG ($P<0.01$), but was without effect on TDG mRNA expression compared to controls. It also increased the excision efficiency of εA and εC ($P<0.001$) compared to controls, however, the effect of the higher dose was less pronounced in all cases ($P<0.01$–$P<0.001$) than for the lower dose.

Conclusions In conclusion, the potential neuroprotective effect of KYNA in brain cells may include the stimulation of DNA repair pathways.

Key words: kynurenic acid, DNA glycosylases, BER pathway, hippocampus, sheep

PERIPHERAL EXPRESSION OF CYTOKINES (IL-1 BETA, IL-6) AND CORTICOSTERONE LEVELS UNDER INDUCED INFLAMMATION IN RATS WITH DIFFERENT BEHAVIOURAL CHARACTERISTICS

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Background A number of recent studies indicate a correlation between the immune system response in various inflammatory processes (bacterial, viral, autoimmune diseases), stress hormones and physical activity.

Purpose The aim of this study was to investigate the effect of induced inflammation induced by LPS administration on IL-1beta, IL-6 and corticosterone levels in behaviorally differentiated rats into high and low motor activity in a novel environment.

Methodology The experiment was performed on rats, male non-breeding Wistar stock. In the novelty test, animals were divided into high (HR) and low (LR) motor activity groups. Within each behavioural group, experimental groups were separated and given an intraperitoneal injection of LPS from *E.coli* (150 µg/kg b.w. in 0.5 ml saline). Control groups received an injection of saline solution. Blood samples collected at three time points (7 days before, 3h and 24h after injection) were used to determine the concentration of the cytokines IL-1beta, IL-6 and corticosterone (by ELISA). The locomotor activity of the animals was also tested in actometers 3h and 24h after injection.

Results Intraperitoneal injection of LPS caused a significant increase in the cytokines IL-1beta and IL-6, as well as an increase in corticosterone concentration observed both 3h and 24h after immunization, more strongly marked in the LR group. There was also a statistically significant decrease in the mean number of horizontal, vertical and ambulatory movements 3h and 24h after LPS injection. This decrease was evident in both the HR and LR groups of animals but was more significant in the LR group.

Conclusions The results indicate that intraperitoneal injection of LPS caused a significant increase in IL-1beta, IL-6 and corticosterone concentrations especially during the acute phase of the inflammatory response. This increase plays a key role during 'sickness behaviour', as evidenced by the reduction in episodes of horizontal and vertical movements especially in LR individuals.

Key words: IL-1beta, IL-6, corticosterone, inflammatory, physical activity

THE EFFECT OF HEXARELIN ON THE MET-ENKEPHALIN SYSTEM IN STRESSED LAMBS

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Background Endogenous opioid peptides, mainly Met-enkephalin, mitigate up-regulation of the hypothalamo-pituitary-adrenal axis during stress response and decrease the risk of serious diseases. Hexarelin is a synthetic analog of Met-enkephalin, growth hormone secretagogue receptor 1a (GHSR) agonist, mainly researched for its effect on growth hormone (GH) release in human and rodent model.

Aim of the study The present study was conducted to assess the effects of isolation stress and/or hexarelin administration on multiple Met-enkephalin related parameters in novel animal model - three month-old lambs.

Methodology Lambs were divided into four groups: control; stressed by 60 min of isolation; injected with hexarelin; stressed and injected with hexarelin. Plasma and hypothalamus were drawn out and directed to analyze levels of cortisol, Met-enkephalin (RIA), mRNA for PENK (RT-PCR), opioid receptors binding.

Results The effect of isolation stress on plasma concentrations of cortisol was markedly delayed in lambs receiving hexarelin. In contrast, the stress induced increase in plasma concentrations of Met-enkephalin were either unaffected or augmented by hexarelin administration. Moreover, the stress induced decrease in hypothalamic Met-enkephalin concentrations was not observed in lambs receiving hexarelin. In addition, hypothalamic release of Met-enkephalin *in vitro* was increased in tissue from stressed lambs and further potentiated by hexarelin. Hypothalamic expression of proenkephalin (PENK) was increased in stressed lambs but the effect was greatly attenuated in stressed lambs receiving hexarelin. Hexarelin also influenced opioid receptors in the hypothalamus.

Conclusions The obtained results for the first time showed that hexarelin interacts with Met-enkephalin modulating the stress response at the central and peripheral level in growing lambs. It is suggested that hexarelin is important factor also during stress responses but research on its effects should be conducted simultaneously with testing opioids profile.

Key words: hexarelin, opioids, PENK, stress, lambs

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43RF-AMIDE - POSSIBLE ACTION ON THE FSH PITUITARY CELLS SECRETORY ACTIVITY. PRELIMINARY RESULTS

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Background 43RF-amide (orexigenic neuropeptide, belonging to RF-amide peptides) is engaged in appetite regulation processes at the central nervous system level. Neuropeptides involved in the regulation of food intake are often involved also in the reproductive processes activity controlling. Therefore it is probable, that 43RFa can participates in the modulation of the FSH pituitary cells secretory activity.

The aim of this study was to verify the research hypothesis, which assume that 43RFa can modulate FSH cells secretory activity in sheep.

Methodology The experiment was performed on sexually mature Polish Merino sheep (n=48). Animals were divided into three groups. The following intracerebroventricular infusions were performed: control group (Ringer-Locke solution), group I (43RFa in dose 10µg/480µl/day), and group II (43RFa in dose 50µg/480µl/day). After the experiment animals were slaughtered: the pituitaries were stored for Real Time RT qPCR or immunohistochemistry and plasma samples were stored for radioimmunoassay analysis.

Results Preliminary results have shown that central infusion of 43RFa at dose of 50µg/480µl/day increase fshβ mRNA ex-

pression in pituitary cells. At the same time no changes in FSH blood concentration were noted after 43RFa treatment in any groups of sheep.

Conclusion The obtained results suggest that 43RFa can modulate the FSH secretory activity in pituitary cells in sheep, but further investigations need to be completed to confirm this hypothesis.

Key words: sheep reproduction, central nervous system, appetite regulation, FSH

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DOES 43RF-AMIDE CAN MODULATE THE PITUITARY LH CELLS SECRETORY ACTIVITY IN SHEEP? PRELIMINARY RESULTS

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Background Reproduction depends on mechanisms responsible for the regulation of energy homeostasis and neuropeptides involved in the regulation of food intake and could be also engaged in the regulation of the gonadotrophic axis activity. 43RF-amide (orexigenic neuropeptide, belonging to RF-amide peptides) is engaged in appetite regulation processes at the central nervous system level.

Aim of the study An *in vivo* model based on intracerebroventricular infusions was used to determine whether centrally administered 43RFa affects transcriptional and translational activity of LH in sheep.

Methodology The experiment was performed on sexually mature Polish Merino sheep (n=48). Animals were divided into three groups. The following intracerebroventricular infusions were performed: control group (Ringer-Locke solution), group I (43RFa in dose 10µg/480µl/day), and group II (43RFa in dose 50µg/480µl/day). After the experiment pituitaries were stored for Real Time RT qPCR or immunohistochemistry and plasma samples were stored for radioimmunoassay analysis.

Results The obtained preliminary results have shown no changes in Ihβ gene expression as well as LH concentration in blood plasma in all investigated groups of sheep.

In conclusion, the present data suggest that 43RFa does not affect LH secretory activity in pituitary cells, but, further studies, especially immunohistochemical determinations, need to be done to confirm the obtained observations.

Key words: sheep reproduction, central nervous system, appetite regulation, LH

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ANALYSIS OF THE EFFECTS OF A NOVEL NEUROPEPTIDE – KISSPEPTIN – ON PERIPHERAL AND CENTRAL MECHANISMS OF METABOLIC DYSFUNCTION IN AN ANIMAL MODEL OF ACTIVITY-BASED ANOREXIA

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Background Anorexia nervosa (AN), as one of the most deadly mental illnesses, is a mosaic of multiple harmonizing etiopathogenetic factors. AN has traditionally been viewed as a disorder of a psychological nature, but the modern model explaining its origin and development has evolved to a form at least partially based on a metabolic component. Neurobiological analysis has recognized a clear dysfunction in adaptive pathways that induce or at least potentiate multisystemic clinical symptoms.

The main aim of this study was to explore the neurobiological basis of AN by assessing the effect of exogenous kisspeptin on the development and course of abnormalities observed in an animal model of activity-based anorexia (ABA).

Methodology A rat model of activity-based anorexia was adapted for this study, in which peripheral and central neurohormonal disturbances were analyzed. Besides, the observation of animal behavior, physical activity, changes in body weight, and food intake, the variability of heart rate and blood pressure were assessed. The collected tissues were processed and subjected to biochemical and histopathological analysis. In addition, using magnetic resonance spectroscopy, we developed a neurochemical profile of the hypothalamus and brainstem. The resulting brain metabolite spectra revealed an imbalance reflecting the effects of ABA on local energy balance and adaptive antioxidant mechanisms. A number of abnormalities involving systemic metabolism, reproductive function, and the cardiovascular system were also demonstrated, largely reflecting the clinical picture of AN.

Results Kisspeptin administered subcutaneously alleviated ABA modeling by altering the pattern of weight loss. In addition, partial normalization of gamma-aminobutyric acid (GABA) and creatine levels (hypothalamus), as well as restoration of basal glutamate levels (brainstem), was achieved in brain centers responsible for the regulation of appetite and satiety.

Conclusion The obtained results indicate that kisspeptin potentially, through modulation of hypothalamic GABA-ergic signaling, increases food intake and thus positively affects brain metabolism.

Key words: anorexia nervosa, activity-based anorexia, kisspeptin, hypothalamus, 1H NMR,

LH SECRETION FROM PITUITARY GLAND OF SEXUALLY IMMATURE COMMON CARP (*CYPRINUS CARPIO* L.) UNDER THE INFLUENCE OF VITAMIN D3

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Background Vitamin D3 (VD3) is essential in many physiological functions, and there is an increasing recognition that VD3 plays a crucial role in the regulation of reproductive processes in mammals.

Purpose The aim of this study was to investigate the direct effect of vitamin D3 on maturation gonadotropin (LH) secretion from the pituitary gland of sexually immature common carp (Cyprinus carpio L.) in vitro.

Methodology The pituitary glands were obtained from 30, 2-year-old sexually immature common carp after decapitation. Collected pituitary glands were washed twice with preincubation medium (containing 2% Ultroser SF and 1% antibiotic-antimycotic) and transferred into 24-well microplate. Each well contained 1 pituitary in 2 mL of pre-incubation medium. Then the plates were covered and incubated for 2 h at 22°C for equilibration. After the pre-incubation period medium was replaced (after washing) with medium containing vitamin D3 at concentrations: 0 (control), 1, 10, 50 and 100 ng mL-1 medium and incubated for 4 h at 22°C. At the end of the incubation period the media were collected and frozen at -20°C until LH determination by ELISA.

Results After 4 hours of pituitary incubation with vitamin D3 at concentrations 10, 50 and 100 ng·ml-1, significant increases in LH concentrations compared to the control media were found. Only the lowest tested concentration of VD3 did not change LH level in comparison with the control group.

Conclusion The obtained results showed the possible direct, stimulating effect of vitamin D3 at the pituitary level in sexually immature common carp, what indicate that also in fish, as in mammals, vitamin D3 may play an important role in the hormonal/neuroendocrine regulation of the reproductive system.

Key words: common carp, gonadotrophins, LH, pituitary gland, reproduction, Vitamin D

THE EFFECT OF CENTRAL INJECTION OF CAFFEINE ON GNRH/LH SECRETION IN FOLLICULAR PHASE EWES DURING AN IMMUNE/ INFLAMMATORY CHALLENGE

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Background Caffeine may adversely affect fertility in females, although the exact mechanism of this caffeine action has not been established. The caffeine receptors are widespread in the region of the hypothalamus which potentially enables this methylxanthine to affect the gonadotropin-releasing hormone (GnRH) secretion. The action of caffeine could be dependent upon the immune status of the organism because the inflammation modulates the expression of caffeine receptors.

Purpose This study was designed to determine the effect of central (icv.) injection of caffeine on GnRH/ luteinizing hormone (LH) secretion in follicular phase ewes during systemic inflammation induced by injection of lipopolysaccharide (LPS).

Methodology The study was performed on adult Blackhead ewes (n = 24) in the follicular phase of the estrous cycle synchronized by Chronogest® CR method. Ewes were divided into four groups of 6 animals: control (Ringer's solution, icv.), LPS-treated (400 ng/kg, iv.), caffeine-treated (3 mg/animal, icv.) and LPS and caffeine-treated. Animals were euthanized 3 hours after central injection and the preoptic area (POA) and anterior pituitary (AP) were collected. The gene expression was assayed by Real-Time PCR. The concentration of GnRH and LH was assayed using ELISA and RIA, respectively.

Results: Caffeine administration did not influence GnRH synthesis in the POA and LH secretion in the AP in ewes not subjected to immune stress. On the other hand, caffeine injection abolished the suppressory effect of inflammation on the GnRH gene expression and increased GnRH concentration in the POA. In the AP, caffeine reduced the negative effect of LPS treatment on GnRHR gene expression and restored LHβ gene expression and circulating LH level to the control values.

Conclusion Central action of caffeine may induce changes in the GnRH/LH secretion, however, its action seems to be dependent upon the immune status of the organism.

Key words: caffeine, GnRH, hypothalamus, pituitary, ewe

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EFFECT OF CENTRAL ADMINISTRATION OF INDOMETHACINE ON ANANDAMIDE-INDUCED GNRH AND GNRH GENE EXPRESSION IN THE HYPOTHALAMUS OF ANESTROUS EWES

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Background Cannabinoids (CBs) have been known to be involved in the regulation of reproductive functions. Because gonadoliberin (GnRH) is a major regulator of reproduction in mammals, it is suggested that CBs may disturb reproduction through actions on the hypothalamic GnRH neurons directly or indirectly by other intermediates such as prostaglandins (PGEs).

Purpose The hypothesis that PGEs are involved in the CBs effect on the GnRH secretion at the hypothalamic level was tested. The study aimed to investigate the influence of intracerebroventricular (icv) injection of anandamide (AEA) alone or with indome-

thacine (IND) – prostaglandin synthesis inhibitor, on the GnRH and GnRH gene expression in the hypothalamus of anestrous ewes.

Methodology The study was performed on 24 adult, Blackhead ewes in the anestrous season (April-May). The animals were randomly assigned to four experimental groups: a control group that received icv injection of Ringer Locke solution, AEA group that received icv injection of AEA solution in dose 30 µM, IND group that received icv injection of IND solution in dose 5µM, AEA +IND group that received icv IND and AEA solutions. The animals were euthanized two hours after treatments. Hypothalamic structures: the preoptic area (POA) and median eminence (ME) were collected to determine GnRH and GnRH gene expression by ELISA and Real-Time PCR methods. Data were analyzed using two-way ANOVA and Tukey's test.

Results The present study demonstrates that IND can reverse the effect of AEA on the GnRH secretion. AEA injected icv increased GnRH gene expression in the ME but not in POA. The stimulatory effect of AEA on GnRH peptide concentration was observed both in the ME and in POA.

Conclusion The presented study showed that anandamide may act centrally in the ovine brain on GnRH secretion influencing GnRH peptide and gene expression in the POA and ME. PGE might be involved in this process.

Key words: gonadoliberin, hypothalamus, ewe, endocannabinoids, prostaglandins

EFFECT OF THE GONADOTROPIN-RELEASING HORMONE ON THE NEUROKININ RECEPTORS EXPRESSION IN PITUITARY CELLS OF GILTS DURING THE ESTROUS CYCLE

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Background Physiological regulations of reproduction processes in females are still a subject of intensive research. Even though the gonadotropin-releasing hormone (GnRH) is recognized as a key factor in these regulations, there are still many gaps in the understating of the reciprocal connections between the GnRH and cells secreting kisspeptin, neurokinins, and dynorphin. Neurokinins (A and B) and their receptors (Tacr2 and Tacr3) are present in organs of the reproductive system, including the pituitary, but their impact on this gland is not fully discovered. Moreover, the influence of GnRH on changes in the expression of Tacr2 and Tacr3 in the anterior pituitary of pigs has not been elucidated so far.

Purpose Thus, this study aimed to examine the effect of GnRH on neurokinin receptor (Tacr2 and Tacr3) gene expression in porcine pituitary cells.

Methodology The pituitary cells were isolated from gilts on days 2-3 (n=4), 8-12 (n=4), 15-16 (n=4) and 18-20 (n=4) of the estrous cycle. The cells were in vitro pre-cultured for 72 h and then incubated for the next 4 h without (control) or with GnRH (100 ng/ml). Total RNA was extracted from the cells and Tacr2 and Tacr3 gene expression was examined by the Real-Time PCR method. Obtained data were analysed by one-way Anova.

Results Tacr2 and Tacr3 mRNA expression in the porcine pituitary cells isolated on days 2-3, 8-12 and 15-16 of the estrous cycle did not change as an effect of GnRH treatment. The expression of Tacr2 was decreased, whereas Tacr3 was increased under influence of the GnRH in pituitary cells isolated on days 18-20 of the estrous cycle.

Conclusion GnRH is involved in the Tacr2 and Tacr3 gene expression regulation in the anterior pituitary lobe of female pigs, but its impact is dependent on the estrous cycle period.

Key words gonadotropin-releasing hormone, neurokinins, pituitary, pigs

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ACUTE AND CHRONIC INFLAMMATION MODULATE ACTH SECRETION IN PIGLETS

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Background Diabetes and obesity are characterized by a hyperactive hypothalamo-pituitary-adrenal (HPA) axis. Additional diseases are associated not only with peripheral-tissue inflammation, but also with neuroinflammation, such as pituitary inflammation.

Purpose The present study was performed to examine the effect of tumor necrosis factor (TNF), one of the inflammatory factor, on the pituitary ACTH secretion during the early stage of induced obesity and diabetes.

Methodology The experiment was carried out on 10 weeks old piglets (n=24). Animals (females) were kept in standard conditions and divided into 4 experimental groups: I- control, II- chronic inflammation (caused by overweight), III- acute inflammation and IV- overweight with acute inflammation. Piglets from I and III groups were fed with a commercial feed whereas animals from II and IV groups received high-calories diet in order to developed overweight. For inducing acute inflammation animals received a single i.p. injection of streptozotocin (100 mg/kg b.w.). 24 hours after injection pituitary was quickly removed and directed to short tissue culture. Tissue fragments were placed in Eagle'a medium and incubate 20 min without (basal release) or with addition of exogenous TNF. Media were directed to estimation of ACTH secretion by RIA.

Results It was observed that inflammation (acute and chronic) increased *in vitro* ACTH release from pituitary (by 250%-350%). In contrast, *in vitro* addition of TNF changed ACTH secretion differently depending on the type of inflammation developed in in vivo condition.

Conclusion The obtained results indicate that pituitary ACTH secretion changed in the first stage of obesity development in young piglets and might contribute to the development of systemic inflammation.

Key words ACTH, inflammation, overweight, TNF