TOXCON

30th ANNIVERSARY

Interdisciplinary TOXICOLOGY CONFERENCE

30th Interdisciplinary Toxicological Conference

The High Tatras
SLOVAKIA

Stará Lesná - Hotel Academia
September 24–26, 2025

Programme & Abstracts

Editor

Mojmír MACH

ORGANISED BY

Slovak Toxicology Society SETOX, Bratislava, Slovakia

Centre of Experimental Medicine,
Institute of Experimental Pharmacology & Toxicology SAS, Slovakia

Czech Society for Experimental & Clinical Pharmacology & Toxicology of the Czech Medical Association of J. E. Purkyně, Czech Republic

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NEONATAL EXPOSURE TO POLYMER NANOCARRIER POLY(ETHYLENE GLYCOL)-BLOCK-POLYLACTIDE METHYL ETHER (PEG-*B*-PLA) ALTERS HYPOTHALAMIC KISS1/GNRH SYSTEM IN INFANTILE FEMALE WISTAR RATS

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The Kiss1 system is a major gatekeeper of reproductive function in mammals from sexual brain differentiation and puberty onset to adult regulation of gonadotropin neurosecretion. Kisspeptins - a family of neuropeptides are produced mainly by neurons at discrete hypothalamic nuclei – arcuate nucleus (ARC, participating in estradiol-(E_2) negative feedback on gonadotropin-releasing hormone/luteinizing hormone surge (GnRH/LH), anteroventral periventricular nucleus (AVPV) and preoptic area (POA) (included in E_2-positive feedback on GnRH pulse generator) among others. The effects of kisspeptins on the gonadotropic axis result primarily from direct stimulatory actions upon the hypothalamic GnRH system. Our recent study demonstrated the adverse effects of short-time neonatal exposure to PEG-*b*-PLA on pubertal development and reproductive function in adult female rats, manifested by early onset of puberty and accelerated reproductive senescence. The aim of this study was investigating the potential adverse effects of neonatal exposure to PEG-*b*-PLA on relative mRNA levels of genes: kisspeptin (*Kiss1*), Kiss1 receptor (*Kiss1r*), GnRH (*Gnrh1*), LH (*Lh*), and estrogen receptor1 (*Esr1*) in ARC, AVPV and POA isolated from the 17-days old infantile females using real-time PCR. Neonatal females were *i.p.* injected with 4, 20 and 40 mg/kg b.w. of PEG-*b*-PLA, vehicle alone (deionized water) and diethylstilbestrol (DES, positive control) on postnatal days 4-7. Analysis of relative levels mRNA in the hypothalamic ARC showed significant changes compared to controls – a decrease in *Kiss1*, *Gnrh1* and *Lh* mRNA (p=0.02; p=0.003; p=0.0001 respectively) by the action of 40 mg/kg b.w. of PEG-*b*-PLA (PEG40). No group differences were observed in the AVPV (all p´s>0.05) except for significant decrease in *Gnrh1* mRNA (p=0.012 in PEG40 and p=0.025 in DES groups). Consistent results were recorded in the POA of female rats treated with PEG40. Significantly higher relative levels of *Kiss1*, *Kiss1r*, *Lh* and *Esr1* mRNA relative to controls were determined (p=0.006; p=0.022; p=0.01; p=0.004 respectively) and increasing levels *Gnrh1* mRNA were observed. Our findings indicate a region-specific adverse effect of neonatal PEG-*b*-PLA exposure on the Kiss1/GnRH system in infantile female rats. These significant changes might contribute to deleterious impact on pubertal development and reproductive function recently recorded in adult females neonatally treated with PEG-*b*-PLA.

Supported by the grants APVV 0404-11, APVV-15-0296 and Internal grant SMU 11/2022-SVG1.

ASSESSMENT OF PROTECTIVE ACTION OF SELECTED PHYTOCHEMICALS AGAINST SILVER NANOPARTICLE-INDUCED NEUROTOXICITY USING *IN VITRO* CELL MODELS

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In recent years, the number of applications and the amount of nanosilver used has increased significantly. Silver nanoparticles (AgNPs) are the most commercialized metal nanoparticles, besides biomedical applications (anti-mycotic, anti-inflammatory, anticancer, diagnostic, drug delivery, dental implant coating, wound healing), they are widely used in consumer products (textiles, cosmetics, paints, etc.). Several *in vitro* and *in vivo* studies have raised concern about the potential neurotoxicity caused by AgNPs, which may trigger oxidative stress in cells. The aim of the present study was to evaluate the potential of phytochemicals with antioxidant and anti-inflammatory properties (curcumin, quercetin, epigallocatechin gallate) to mitigate the neurotoxic effects of AgNPs using the human neuroblastoma cell line SH-SY5Y and the immortalized mouse hippocampal cell line HT22. SH-SY5Y (ECACC 94030304) and HT22 (SCC129) cells were cultured in DMEM/F12 and DMEM media, respectively, supplemented with antibiotics, glutamine and 10% FBS in the presence of AgNPs (0.1–10 µg/ml) of different sizes (10, 100 nm) with or without tested phytochemicals (1-100 µM) for different times depending on the assay used (6-72 h). We used three different treatment approaches: pre-treatment, co-treatment and post-treatment of AgNPs with phytochemicals. Cell viability was assessed by detection of mitochondrial activity based on the reduction of tetrazolium dye MTT and membrane integrity measuring lactate dehydrogenase (LDH). The levels of intracellular reactive oxygen species (ROS) were measured using fluorescent probe 2' 7'-dichlorodihydrofluorescein diacetate (DCFDA). Exposure of SH-SY5Y and HT22 cells to AgNPs of both size induced concentration- and time-dependent inhibition of cell viability and increase of LDH activity and ROS production. Despite the confirmed antioxidant properties of phytochemicals, none of the tested compounds showed a protective effect against nanoparticle-induced cytotoxicity under the given experimental conditions. HT22 cells were more sensitive to the effect of nanoparticles as well as phytochemicals.

Supported by the grant VEGA 2/0156/24.

ISSN: 1337-6853 *(print version)* | 1337-9569 *(electronic version)*

GJIC ASSESSMENT INDICATES NOVEL TOXIC AND CARCINOGENIC THREATS FROM THE INVASIVE WATER BLOOM CYANOBACTERIUM *RAPHIDIOPSIS RACIBORSKII*

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Raphidiopsis (Cylindrospermopsis) raciborskii is an invasive, bloom-forming cyanobacterium originally described in tropical regions, but now increasingly present in temperate zones, posing ecological and public health hazards. Strains of *R. raciborskii* differ in toxin production: Australian and Asian strains produce the highly potent cytotoxin cylindrospermopsin (CYN), while South American and Southeast Asian isolates may produce neurotoxic saxitoxins (SXTs). In contrast, European and Mediterranean strains appear to lack these well-characterized cyanotoxins, and their toxicological properties and hazards remain poorly understood. This study compared five *R. raciborskii* strains: two Australian CYN-producing strains (CS-505, CS-506), and three CYN-nonproducing strains - an Israeli strain (Lake Kineret, KLL07) and two Polish isolates (UAM/DH-PnRr from Pniewskie Lake and UAM/DH-KmRr from Kierskie Małe Lake). LC-HRMS analysis revealed distinct profiles of secondary metabolites among the five strains. Despite differences in CYN production, aqueous methanolic extracts from both Australian CYN-producing and Polish CYN-nonproducing strains showed comparable *in vitro* cytotoxicity in WB-F344 rat liver cells, while the KLL07 strain was less potent. Importantly, all extracts disrupted gap junctional intercellular communication (GJIC) at non-cytotoxic concentrations, albeit with varying potencies. GJIC is essential for maintaining tissue homeostasis, and its inhibition is a recognized hallmark of tumor promotion via nongenotoxic mechanisms. Extracts from CS-506, PnRr, and KmRr rapidly suppressed GJIC within 30 min. The effect of KmRr on GJIC was transient, whereas its cytotoxicity progressed. In contrast, extracts from CS-505, CS-506, and PnRr exhibited a time-dependent increase in GJIC inhibition, with potencies 3–10 times greater than that of the KLL07 strain. These findings indicate that even CYN-nonproducing *R. raciborskii* strains can produce other bioactive compounds capable of disrupting GJIC and potentially promoting carcinogenic processes. The observed GJIC inhibition supports further investigation into the identification and of *R. raciborskii* metabolites, their role in cancer-related pathways and carcinogenic hazards.

This project was co-financed by the Governments of Czechia, Hungary, Poland and Slovakia through Visegrad Grants from International Visegrad Fund (grant no. 22320076 – CyanoMeta), and supported by the Czech Science Foundation (GAČR) under grant no. GA24-12116S.

MULTI-YEAR STUDY MONITORING THE MERCURY CONTENT IN THE TISSUES OF CATTLE AND SMALL RUMINANTS SAMPLED IN THE CZECH REPUBLIC BETWEEN 2014 AND 2023

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Mercury is a very important environmental contaminant. Analyses of mercury concentrations in the muscle, liver and kidneys of cattle, sheep and goats were conducted in the Czech Republic during the period from 2014 to 2023. The average mercury content in muscles, livers and kidneys of calves (N=71) was 0.5±0.00 µg/kg, 2.7±0.5 µg/kg and 4.1±0.8 µg/kg, respectively. In fattening cattle (N=158), the average mercury content in muscles, livers and kidneys was 0.5±0.00 µg/kg, 2.1±0.2 µg/kg and 4.9±0.3 µg/kg, respectively. In cows (N=282), the average mercury content in muscles, livers and kidneys was 0.5±0.00 µg/kg, 2.3±0.1 µg/kg and 6.9±0.3 µg/kg, respectively. In all age categories the highest mercury concentrations were found in the kidneys, lower in the livers and the lowest in the muscles. When comparing the age groups, significantly higher mercury concentrations in kidneys were observed in cows than in calves and fattening cattle. The mercury content in sheep (N=30) varied from 0.02 µg/kg in muscle to 17.3 µg/kg in kidney. The significantly highest mercury content was found in the kidneys (5.4±0.8 µg/kg) and liver (4.7±0.8 µg/kg) in comparison to muscle (0.5±0.0 µg/kg). The mercury content did not differ significantly between lambs and sheep in any tissue. In case of goat (N=11), mercury content found in goat samples ranged from 0.2 to 10.0 µg/kg. The significantly highest mercury concentration was found in the kidney (3.5±0.9 µg/kg) and in liver (1.7± 0.7 µg/kg) in comparison to muscle (0.4±0.1 µg/kg). The maximum residual limit for human consumption was exceeded in 10 kidney samples (3 calves, 6 cows, 1 fattening cattle) and in 1 liver sample (calf) but was not exceeded in any sheep and goat samples. It