РЕЗЮМЕТА

на отпечатаните в пълен текст научни трудове на доц. д-р Галя Ставрева, д.м.

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А1 **Ставрева Г.** Автореферат за дисертационен труд за придобиване на ОНС „Доктор“ на тема: Фармакологични аспекти на модуларни и низходящи отговори в ректоанална област

Annotation

Background: Disorders in the evacuation function of the gastrointestinal tract are a significant medical and social problem. Therefore, an increasing number of experimental and clinical studies have focused on nervemediated motor activity of the recto-anal region. It is accepted now that the rectoanal evacuation activity is a complex process involving voluntary control of excretion as well as autonomic innervation of rectum and internal and external anal sphincters. Objective: The aim of this study was to characterize the contribution of major neurotransmitter systems to modular and descending motor responses in Wistar rat rectoanal region.

Methods: Mechanographic on-line technique, partitioned organ bath, electrical field stimulation (EFS; 0.8 ms; 40 V; 2, 5 or 10 Hz; 20 s) or distension were used to evaluate motor responses of circular and longitudinal muscles of rectum and anal canal in rat rectoanal preparation as a display of excitation of modules of nerve networks or descending pathways. Drugs were used to characterize the contribution of cholinergic, nitrergic, tachikyninergic, and purinergic neurotransmissions to modular networks and descending pathways in a rat experimental model. Immunohistochemical and histochemical techniques were used to study the presence and distribution of choline acetyltransferase, substance P, ATP-synthase and NADPH-diaphorase in neuronal structures of the myenteric plexus of rat anorectum.

Results: Twitch-like frequency-dependent contractions, more pronounced in distal rectal preparations, characterized the modular motor responses of rectal circular muscle rings and anal

canal. The motor activity of internal anal sphincter depended on the frequency of stimulation and varied from deep long-lasting relaxation to an initial short-lasting relaxation followed by a contraction. The responses were significantly less pronounced as compared with those of longitudinal muscle strips. In the presence of atropine (0.3 μM), the contractions of rectal rings decreased, the relaxation of internal anal sphincter increased, and inhibition of the contractions of the anal canal, followed by relaxation was observed. NG-nitro-L-arginine (0.5 mM) increased the contractile responses and suppressed the relaxations of the internal anal sphincter. L-arginine (0.5 mM) decreased the contractions and extended the relaxations of the internal anal sphincter and anal canal. In entire recto-anal preparation, application of EFS to distal rectum elicited descending contractile response (5.16±0.46 mN) of anal canal, while distension by balloon induced descending response that consisted of contraction (1.50±0.18 mN) followed by relaxation (3.12±0.34 mN). In the presence of atropine, the EFS-elicited descending contractions of the anal canal were suppressed, and a relaxation occurred. The initial contraction component of the distension-induced response was decreased, while the relaxation remained unchanged. Spantide (0.1 μM) lowered the contractile component of the anal canal response even more. NG-nitro-Larginine enhanced the contraction, prevented the atropine-dependent relaxation of the EFS-elicited response and inhibited the distension-induced relaxation. L-arginine suppressed the contraction and extended the relaxation. The electrically- and balloon-evoked responses of anorectal preparations were tetrodotoxin (0.1 μM)-sensitive. ChAT-, substance P-, NADPH-diaphorase- and ATP-synthase-positive nerve fibers and NADPH-diaphorase-positive perikarya were found in myenteric ganglia of the anal canal.

Conclusion: The results obtained suggest that cholinergic and nitrergic systems are not equally involved in modular nerve networks in different regions of anorectum. Cholinergic neurotransmission, more expressed in distal rectum, underlies the contractile potency of rectal circular muscles, while nitric oxide-dependent neurotransmission(s) control the relaxation ability of internal anal sphincter and anal canal. The results show that excitatory neurotransmission(s), more expressed to longitudinal muscle, dominate in the local recto-anal nerve networks. Our findings suggest activation-dependent descending reflex motority of the anal canal, involving electrical stimulation-displayed cholinergic and tachykininergic, as well as distension-manifested nitrergic neuro-muscular communications.

Key words: rat anorectum, descending motor response, modular motor response, atropine; L-arginine; NGnitro-L-arginine, ATP, spantide

B1. **Stavreva G**, Ivancheva C, Radomirov R. Ellectrically- and distension-dependent reflex pathways controling the motor activity of anal canal. Comptes rendus de l'Academie bulgare des Sciences. 2013;66(9):1285-1290. ISSN 1310–1331 (Print); ISSN 2367–5535 (Online) **IF 0.198; SJR 0.205, Q2**

Abstract

The motor responses of anal canal in rat experimental model were followed as a display of the controlling role of descending recto-anal reflex pathways on contraction/relaxation events underlying the evacuation activity. The nerve structures in the entire recto-anal segment-preparation mounted in two-compartment organ bath were excited by electrical stimulation applied to the rectum or the anal canal and by balloon-induced distension of the proximal or the distal rectal wall. Electrical field stimulation (0.8 ms, 40 V, 5 Hz, 20 s) applied to the rectum elicited twitch-like descending contractile response of the anal canal. More pronounced contraction was observed when the electrical stimuli were applied directly to the anal canal. The motor activity of the anal canal evoked by balloon inflation in the rectum differed depending on the locality of the application of distension along the rectum. The anal canal responded by descending contraction or by short-initial contraction followed by relaxation when the distension was applied to proximal or

to distal part of the rectum, respectively, indicating an essential role of mechanoceptors in activation of long excitatory and short inhibitory descending recto-anal motor reflex pathways.
Key words: recto-anal region, descending motor reflexes

B2. Simeonova L, **Stavreva G**, Nedialkova N, Negrev N, Kadinov B, Radomirov R. Local nerve networks-mediated activity of colo-rectal longitudinal and circular muscles in rat model. Comptes Rendus de L'Academie Bulgare des Sciences, 2013; 64 (3):437-442. ISSN 1310–1331 (Print) ISSN 2367–5535 (Online) **IF 0.198; SJR 0.205, Q2**

Abstract
Mechanographic on-line technique and electrical field stimulation (0.8 ms, 40 V, 2 Hz, 20 s) were used to evaluate the motor responses of longitudinal and circular muscles isolated from rat colon and rectum as model preparations to display excitation of local enteric nerve networks in the large intestine. The local responses of longitudinal muscle strips isolated from proximal and distal parts of the colon and rectum were contractions. There were no differences between the peak amplitude in the motor responses of the longitudinal muscles which belonged to the colon or to the rectum. The modular contractile responses of the circular muscle rings from both parts of the colon and the middle part of the rectum were significantly less pronounced than the local responses of the longitudinal muscle strips. The electrically-induced responses of the colonic and rectal muscles were tetrodotoxin (0.1 μM)-sensitive. The results show that low frequency-sensitive excitatory neurotransmission more expressed to the longitudinal muscle dominates in the local nerve networks of the rat colon and rectum suggesting an essential role of colo-rectal contractile mechanisms in propelling the gut content in anal direction.
Key words: local nerve networks, colon, rectum

B3. Nedialkova N, **Stavreva G**, Negrev N, Radomirov R. Characterization of colonic ascending and descending reflex motor activity. Comptes rendus de l'Academie bulgare des Sciences. 2013;66(9):1279-1284. ISSN 1310–1331 (Print), ISSN 2367–5535 (Online) **IF 0.198, SJR 0.206, Q2**

Abstract

Electrically-elicited ascending and descending motor responses of longitudinal and circular muscles in experimental model of isolated segments of rat colon were recorded to characterize the involvement of orally and anally directed reflex pathways in underlying the motility of colonic region of the large intestine. Rectangular electrical stimuli (0.8 ms, 40 V, 5 Hz, 20 s) applied to the middle part of the segment-preparations placed in three-compartment organ bath evoked tetrodotoxin (0.1 μM)-sensitive ascending contractions in the longitudinal and circular muscles of the proximal part of the colonic segments that were more pronounced as compared to the descending contractions of the longitudinal muscle and relaxation followed by contraction in the circular muscle belonging to the distal region of the preparations. The results indicate that locally-applied electrically-induced excitation activates synchronously by one and the same stimulus ascending and descending motor reflex pathways and characterizes the excitatory ascending motor pathways as nerve structures dealing essential role in the contractile potency of both longitudinal and circular muscles as compared to the inhibitory ability of the descending motor pathways supply the circular muscle.
Key words: ascending motor reflexes, descending motor reflexes, circular muscle, longitudinal muscle

B4. **Stavreva GT**, Gorcheva ZV, Negrev NN, Radomirov RG. Cholinergic,

tachykininergic and nitrergic transmission in ascending motor activity of colonic longitudinal muscle in a rat model. Comptes Rendus de L'Academie Bulgare des Sciences. 2016; 69 (3):357-364. ISSN 1310–1331 (Print), ISSN 2367–5535 (Online); **IF 0.251, SJR 0.209, Q3**

Abstract

The purpose of the present study was to examine in vitro the motor activity of longitudinal muscle (LM) based on local neuronal circuitry and ascending reex pathways. The electrically-induced local and ascending motor responses of rat colonic LM were studied using partitioned three-compartment organ bath, electrical field stimulation (0.8 ms, 40 V, 5 Hz, 20 s) and mechanographic on-line recording techniques. To establish the role of excitatory and inhibitory neurotransmissions in the reex pathways, the motor activity was studied by cholinergic-, tachykininergic- and nitrergic-related drugs. Atropine (0.3 μM) added in the oral compartment of the bath considerably decreased the amplitude of ascending contractions of the LM provoked by electrical stimulation (5:4 _ 0:6 mN, n = 10, p < 0:05). During atropine treatment spantide (0.1 μM) further signi_cantly suppressed the ascending contractile motor responses (3:2 _ 0:3 mN, n = 8, p < 0:05). L-NNA (0.5 mM), an inhibitor of nitric oxide synthase increased the contractions during atropine treatment, while L-arginine (0.5 mM) decreased the amplitudes of contractile responses. Atropine inhibited the ascending contractile responses of the LM of colonic segments indicating the essential stimulatory role of the cholinergic system in the colonic contractility. The present experiments also demonstrated the in-volvement of tachykininergic and nitrergic neurotransmission in the ascending motor responses of the colonic LM.

Key words: L-arginine, ascending motor response, atropine, NG-nitro-L-arginine, rat colon, spantide

B5. Gorcheva Z, **Stavreva G**, Radomirov R. Neurotransmitter implications in descending motility of longitudinal and circular muscles in rat colon. Archives of the Balkan Medical Union. 2018; 53, (1):9-17. ISSN 1584-9244; **SJR 0.192 Q3**

Abstract

Introduction. The role of neurotransmitter systems in the motor activity of longitudinal or circular muscles in autonomic regulation of the motility of the colon by the nervous system is unclear. The aim of the study was to investigate the neurotransmitter implications in descending motility of longitudinal and circular muscles in rat colon.

Methods. Electrically-induced (2, 5 or 10 Hz, 0.8 ms, 40 V, 20 s) local or descending motor responses of longitudinal and circular muscles in isolated preparations and drugs were used to define the neurotransmitters' role in colonic motility.

Results. The spontaneous activity of the distal part of preparations manifested as high-amplitude irregular contractions more expressed in the longitudinal muscles. The electrically-induced local responses differed considerably in the two muscles: in longitudinal muscle there were frequency-dependent contractions, while initial relaxation followed by contraction was observed in circular muscle. The descending motor response resembled the pattern of the local responses, but the amplitudes were significantly less expressed, as compared to the respective local responses. In atropine-pretreated (0.3 μM) preparations, the contractions of longitudinal and circular muscle significantly decreased, and initial relaxation preceded the contractions of the longitudinal muscle. In the presence of atropine, spantide (0.1 μM) reduced more noticeably the contractile components of responses in both muscles. L-NNA (0.5 mM) restored to a great extent the descending contractions of the longitudinal and circular muscles, while L-Arginine (0.5 mM) strongly depressed the contractions and more significantly increased the relaxation in circular muscle.

Conclusions. The present results suggest the implication of both cholinergic and tachykininergic

systems as excitatory neurotransmissions in the colonic descending reflex pathways and the involvement of nitrergic neurotransmitter systems in the descending inhibitory neuromuscular signalization predominantly serving the circular muscle.

Key words: atropine, L-arginine, NG-nitro-L-arginine, spantide, descending reflex pathways, rat colon.

B6.. Brinkman DJ, Tichelaar J, Mokkink LB, Christiaens T, Likic R, Maciulaitis R, Costa J, Sanz EJ, Maxwell SR, Richir MC, van Agtmael MA... Kostadinova I, Ganeva M, Atanasova I, Gatchev E, **Stavreva G**...for the Education Working Group of the European Association for Clinical Pharmacology and Therapeutics (EACPT) and its affiliated Network of Teachers in Pharmacotherapy (NOTIP) Key learning outcomes for clinical pharmacology and therapeutics education in Europe: A modified Delphi study. Clin Pharmacol Ther. 2018 Aug;104(2):317-325. doi: 10.1002/cpt.962; **IF 6.336; SJR 1.842, Q1**

Harmonizing clinical pharmacology and therapeutics (CPT) education in Europe is necessary to ensure that the prescribing competency of future doctors is of a uniform high standard. As there are currently no uniform requirements, our aim was to achieve consensus on key learning outcomes for undergraduate CPT education in Europe. We used a modified Delphi method consisting of three questionnaire rounds and a panel meeting. A total of 129 experts from 27 European countries were asked to rate 307 learning outcomes. In all, 92 experts (71%) completed all three questionnaire rounds, and 33 experts (26%) attended the meeting. 232 learning outcomes from the original list, 15 newly suggested and 5 rephrased outcomes were included. These 252 learning outcomes should be included in undergraduate CPT curricula to ensure that European graduates are able to prescribe safely and effectively. We provide a blueprint of a European core curriculum describing when and how the learning outcomes might be acquired.

B7 Gorcheva ZV, **Stavreva GT**, Negrev NN, RadomirovRG. Ascending excitatory and inhibitory motor activity of colonic longitudinal and circular muscles in rat model. J Biomed Clin Res. 2019;12(1):10-8. ISSN 1313-9053 (НАЦИД)

Summary

In this experiment we studied the role of excitatory and inhibitory neurotransmissions in the ascending reflex pathways in isolated rat colon. Partitioned organ bath, electrical field stimulation (EFS), drugs and isolated preparations were used to evaluate motor activity of (LM) and circular muscles (CM). Ascending motor responses of LM and CM were frequency-dependent contraction, significantly more expressed in LM. Atropine (0.3 μM) decreased ascending contractions of LM. During atropine treatment spantide (0.1 μM) further suppressed ascending contractile motor responses. In the presence of atropine, L-NNA (0.5 mM) restored ascending contractions of LM, while contractions were strongly depressed after addition of L-arginine (0.5 mM). Ascending response in CM, caused by atropine, consisted of an initial relaxation followed by contraction. Spantide decreased the contraction. L-NNA reduced the relaxation and significantly restored the atropine-influenced contraction, while L-arginine induced a deep relaxation of CM. The presence of ChAT, SP-containing nerve cell bodies and fibers and NADPH-diaphorase-reactive cell bodies and processes in myenteric ganglia were detected. The results indicated that nitric oxide is an important modulator of ascending cholinergic and tachykininergic excitation in colonic region of the large intestine of rats.

Key words: ascending reflex, rat colon, atropine, L-arginine, L-NNA, spantide

B8. Gorcheva ZV, **Stavreva G**, Dikova N, Negrev N, Radomirov RG. Neurotransmissions contributing to ascending reflex responses of colonic circular muscle in a rat model.C. R. Acad. Bulg. Sci. 2019;72(9):1276-83.*ISSN* 1310-1331**; IF 0.343, SJR 9.218, Q2**

Abstract

Electrical field stimulation (0.8 ms, 40 V, 2–5–10 Hz, 20 s) applied at the oral or the distal part of isolated segments of rat colon mounted in twocompartments organ bath was used to excite the nerve structures mediating the local or ascending responses of the circular muscle. To evaluate the neurotransmissions involved in the ascending reflex pathways the ascending motor responses were studied by cholinergic, tachykininergic and nitrergic-related drugs. The electrically-induced ascending responses of the colonic circular muscle were frequency-dependent contractions. Atropine (0.3 μM) added to the oral compartment of the bath converted the ascending contractions of the circular muscle induced by stimulation applied at a frequency of 5 Hz to motor responses consisting of an initial relaxation followed by a contraction (atropine-mediated contraction of 2.0±0.24 mN vs. control of 4.1±0.6mN, $p < 0.05$). Spantide (0.3 μM), added in the presence of atropine reduced the contraction more without changing the relaxation indicating that besides cholinergic, the tachykininergic neurotransmission is presented in ascending stimulatory motor responses. L-NNA (0.5 mM) reduced the relaxation and significantly restored the atropinedecreased contraction while L-Arginine (0.5 mM) provoked a deep relaxation in atropine-pretreated colonic segments, thus suggesting modulation role of inhibitory nitrergic neurotransmission in excitatory ascending reflex pathways of colonic circular muscle.

Key words: rat colon, neurotransmission, ascending motor responses

B9. Dikova NN, **Stavreva GT,** Prisadova NA, Radomirov RG. Non-adrenergic non-cholinergic ascending reflex motility of colonic longitudinal and circular muscles. Comptes rendus de l academie bulgare des sciences. 2020;73(4): 559-68 ISSN 1310–1331 (Print), ISSN 2367–5535 (Online**); IF 0.378; SJR 0.244, Q2**

Abstract

Because of high medical and social impact of the diseases of intestinal system the contribution of neurotransmitter systems to the peristaltic activity of large intestine is a matter of experimental and clinical interest. Electrical field stimulation (0.8 ms, 40 V, 2, 5 or 10 Hz, 20 s), partitioned organ bath and drugs were used aiming to display non-adrenergic non-cholinergic motility in isolated colonic segment-preparations in rat experimental model. The application of electrical stimulation to the middle or to the distal part of the colonic segments elicited ascending motility of the proximal part of the preparations due to excitation of the ascending reflex pathways serving the longitudinal and circular muscles. Both muscle layers responded with frequency-dependent contractions as the contractions of the longitudinal muscle were significantly more expressed as compared to those of the circular muscle (12.8 ± 1.3 mN vs. 6.3 ± 0.5 mN, at 5-Hz stimulation). Tetrodotoxin (0.1 μM) prevented the electrically-induced ascending motor responses of both muscles indicating their neurogenic nature. Cholinergic and adrenergic receptors-related drugs were used to indicate the effects of non-adrenergic non-cholinergic neurotransmissions on the ascending motility. In atropine-pretreated (0.3 μM) preparations the contractions of longitudinal and circular muscle significantly decreased and an initial relaxation preceded the contractions of the circular muscle (1.1±0.1 mN and 4.1±0.3 mN, respectively). In the presence of additionally added propranolol (0.1 μM) and prazosin (0.1 μM) the ascending reflex responses of both muscles induced by electrical stimulation applied at a distance of 10 mm consisted of an initial relaxation followed by contraction as the responses of the longitudinal muscle were lower by amplitude. Relaxation without contraction characterized the electrically-evoked ascending responses of longitudinal and circular muscles recorded at a distance of 20 mm from the excited distal part of the segmentpreparations

suggesting the presence of longer inhibitory and shorter stimulatory pathways of non-adrenergic non-cholinergic neurotransmissions involved in the colonic ascending neuromuscular connections.
Key words: rat colon, ascending reflex responses, non-adrenergic noncholinergic neurotransmissions

B10. Prisadova NA, Gorcheva Z, **Stavreva GT**, Ardasheva R, Radomirov RG. Non-adrenergic non-cholinergic descending reflex motility. Comptes rendus de l academie bulgare des sciences. 2021; in press. ISSN 1310–1331 (Print), ISSN 2367–5535 (Online); **IF 0.343, SJR 0.194 Q3**

Abstract
The motility of distal part of isolated colonic segments evoked by electrical stimulation applied to distal or to proximal part of colonic preparations in a rat experimental model was considered as response based on the excitation of the local neuronal circuitry or as a display of excitation along the descending reflex pathways. The electrically-induced local or descending motor responses were studied using three-compartment organ bath, electrical field stimulation (EFS) and mechanographic on-line recording techniques. The electrically-elicited colonic motility was tetrodotoxin (0.1 μM)-sensitive indicating its neurogenic nature. To evaluate the declination of excitation along descending reflex pathways the descending motor responses were compared to the local responses of distal part of the colonic segments. EFS induced local and descending frequency-dependent contractions of longitudinal muscle. The local responses were significantly more pronounced by magnitude. The local and descending responses of the circular muscle were similar by pattern and consisted of an initial relaxation followed by contraction. The amplitude of relaxations in both responses did not differ considerably, whereas the contractile components were significantly different. To determine the involvement of non-adrenergic non-cholinergic (NANC) neurotransmissions in the descending reflex pathways the descending motor responses of both muscles to 5-Hz EFS were evaluated in the presence of adrenergic- and cholinergic-blocking drugs. Atropine (0.3 μM) added to the distal part of colonic preparations converted the descending response of the longitudinal muscle from contractions to biphasic responses consisting relaxation and contraction and considerably decreased the contractile components in the descending responses of both longitudinal and circular muscle muscles. In the presence of atropine, propranolol (0.1 μM) and prazosin (0.1 μM) the NANC contractile components of descending responses of colonic longitudinal and circular muscles were further significantly suppressed while the NANC relaxations of both muscles were not influenced indicating that rather relaxation ability than contractile potency underlie the descending reflex NANC neuromuscular communications in longitudinal and circular muscles along the colonic section of large intestines.
Key words: NANC descending reflex motility, rat colonic muscles

Г1. Valcheva-Kuzmanova S, **Stavreva G,** Dancheva V, Terziev L, Atanasova M, Stoyanova A, Dimitrova A, Shopova V. Effect of Aronia melanocarpa fruit juice on amiodarone-induced pneumotoxicity in rats .Pharmacognosy Magazine. 2014; 10 (38), pp. 132-140. ISSN: Print 0973-1296, Online 0976-4062 DOI: 10.4103/0973-1296.131024; **IF 1.256; SJR 0.512, Q4**

Abstract
Background: The fruits of *Aronia melanocarpa* (Michx.) Elliot is extremely rich in biologically active polyphenols. Objective: We studied the protective effect of *A. melanocarpa* fruit juice (AMFJ) in a model of amiodarone (AD)-induced pneumotoxicity in rats.
Materials and Methods: AD was instilled intratracheally on days 0 and 2 (6.25 mg/kg). AMFJ (5 mL/kg and 10 mL/kg) was given orally from day 1 to days 2, 4, 9, and 10 to rats, which

were sacrificed respectively on days 3, 5, 10, and 28 when biochemical, cytological, and immunological assays were performed.
Results: AMFJ antagonized AD-induced increase of the lung weight coefficient. In bronchoalveolar lavage fluid, AD increased significantly the protein content, total cell count, polymorphonuclear cells, lymphocytes and the activity of lactate dehydrogenase, acid phosphatase and alkaline phosphatase on days 3 and 5. In AMFJ-treated rats these indices of direct toxic damage did not differ significantly from the control values. In lung tissue, AD induced oxidative stress measured by malondialdehyde content and fibrosis assessed by the hydroxyproline level. AMFJ prevented these effects of AD. In rat serum, AD caused a significant elevation of interleukin IL-6 on days 3 and 5, and a decrease of IL-10 on day 3. In AMFJ-treated rats, these indices of inflammation had values that did not differ significantly from the control ones.
Conclusion: AMFJ could have a protective effect against AD-induced pulmonary toxicity as evidenced by the reduced signs of AD-induced direct toxic damage, oxidative stress, inflammation, and fibrosis.
Key words: *Aronia melanocarpa*, amiodarone, pneumotoxicity, rats

Г2. Данчева В, **Ставрева Г**, Терзиев Л. Блеомицин-индуцирана белодробна фиброза, механизми. Български медицински журнал. 2016; X(1):14-21 ISSN 1313-1516 (НАЦИД)

Резюме
При повече от 10% от пациентите, лекувани с блеомицин, може да се проявят специфични нежелани реакции в белите дробове. Механизмите в основата на индуцираната от лекарството белодробна фиброза не са напълно изяснени. Дефицитът на ензима, отговорен за метаболизма на блеомицина до нетоксични молекули, окислителни увреждания, про- и антиинфламаторни цитокини имат участие в развитието на интерстициалната белодробна болест. В обзора се разглеждат основните патогенетични механизми, водещи до дисбаланс в процесите на образуване на колаген и колагенолизата, натрупване на съединителна тъкан и нарушена функция и смутен газообмен в белите дробове. Собствени резултати за пневмотоксичните промени след интратрахеалноприложение на блеомицин в доза 2.5 mg/kg при бели плъхове са сравнени и анализирани.
Ключови думи: блеомицин, фиброза, интерстициална белодробна болест, цитокини

Г3. Kamenova K, Lazarov L, Bogdanov G, Handzhieva-Darlenska T, **Stavreva G**, Pendicheva D, Dimitrova D, Metodieva R, Dobrevska G, Boyadzhieva N. The TNF-α M IL-1β Serum levels in men and women with different-degree obesity and prediabetes. General Medicine. 2016; 18 (1):29-31. ISSN 1311–1817; **SJR 0.122, Q4**

Summary
Obesity is one of the reasons for the development of insulin resistance and diabetes mellitus type 2. The mechanisms of both pathological conditions (obesity and diabetes) include the role of infl ammation. It is well documented that the cytokines TNF-α and IL-1β play a role as a pro-infl ammatory cytokine in mechanisms of infl ammation. Other cytokines are also considered in obesity and prediabetes, but TNF-α and IL-1β have most signifi cant participation in mechanisms of obesity. In addition, it is documented that interleukin 1 (IL-1) act as a local mediator of infl ammation, leading to edema, movement of the leucocytes to focus, and entering the bloodstream it leads to increased production of neutrophilic leukocytes from the bone marrow, affects the secretion of other infl ammatory proteins (acute phase proteins from liver), increases the decay of proteins in muscle, increases body temperature (fever) through an action on the central

temperature regulation in the hypothalamus.

Key words: obesity, diabetes mellitus type 2, prediabetes, TNF-α, IL-1β

Г4. Kamenova K, Lazarov L, Bogdanov G, Handzhieva-Darlenska T, **Stavreva G,** Pendicheva D, Dimitrova D, Dobrevska G, Metodieva R, Getova D, Boyadzhieva N. Plasma levels of leptin, ghrelin, and adiponectin in male and femal patients with obesity and prediabets. General Medicine. 2016; 18 (3):8-12. ISSN 1311–1817; **SJR 0.122, Q4**

Summary

Obesity is a chronic metabolic disease which is characterized by a long-term positive energy balance, and an accumulation of an excess fat tissue in the body. Regulation of metabolism and appetite is a complex inter-linked process. The main hormones involved in the regulation of the appetite are leptin, adiponectin and ghrelin. Leptin and adiponectin are adipokines secreted by the fat tissue which decrease appetite. Ghrelin is a hormone secreted by the stomach mucosa that increases appetite in correlation with food intake. The aim of the present study is to establish the plasma levels of leptin, adiponectin and ghrelin in subjects with obesity and prediabetes that are on a low-calorie diet combined with probiotic from three regions in Bulgaria. Our results demonstrate decreased leptin levels and increased ghrelin and adiponectin plasma concentrations according to the subject's body mass index. These data are a novelty into the understanding of the balance between leptin, adiponectin and ghrelin in subjects with different level of obesity. The difference in the hormonal levels could give a light on the mechanisms in appetite dysregulation and the level of reduction of body weight.

Key words: obesity, prediabetes, leptin, adiponectin, ghrelin

Г5. TodorievaTodorova DK, Kovacheva K, Tzvetkov N, Trifonov S, **Stavreva G**, Rashev T, Todorov A, Ivanov P. Study on the role of thrombophilic genetic disorders as a risk factor for thrombotic complications in patients with myeloproliferative disorders. J Biomed Clin Res. 2019;12(1):19-26.ISSN 1313-9053 (НАЦИД)

Summary

Myeloproliferative neoplasms (MPN) are haematological diseases, characterized by clonal hematopoiesis. Hemostasis abnormalities are among the most critical and frequent complications, affecting the quality of life and a possible reason for death. Thrombotic complications are common and multifactorial. Our aim was to study some genetic thrombophilia factors – Factor V Leiden (FVL), G20210A mutation in prothrombin gene (PR G20210A) and PLA2 allele polymorphism of glycoprotein IIIa gene (GPIIIa gene), and their frequency and association with thrombotic risk in both Philadelphia-positive and Philadelphia-negative MPN – chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary and secondary myelofibrosis (MF). In our patient population, PLA2 allele polymorphism of GPIIIa gene proved to be the most common and significantly associated with thrombotic complications – 26.85% of our patients were carriers, and 24.14% of them reported thrombotic complications.

Key words: genetic thrombophilia, myeloproliferative neoplasms, thrombotic complications

Г6. **Stavreva GT**, Dancheva VY, Terziev LG., Krastev PK. Effects of 21-aminosteroid U-74389G on amiodarone-induced pulmonary toxicity in rats. Archives of the Balkan Medical Union. 2019;54(3):404-10.ISSN 1584-9244, **SJR 0.218, Q3**

Abstract

Introduction. The widely used antiarrhythmic amiodarone (AD) has been linked to many health

problems, including pulmonary toxicity. The objective of the study. In the present study we assessed the protective effect of 21-aminosteroid U-74389 G due to its antioxidative and membrane-stabilizing potency on amiodarone-induced pneumotoxicity in rats.
Material and methods. The study was carried out on 72 male Wistar rats, divided into four groups: (1) – control; (2) – treated with AD intratracheally; (3) – treated with AD and U-74389G; (4) – treated with U-74389G alone. AD was instilled twice on days 0 and 2 (6.25 mg/kg with a concentration 3.125 mg/mL). U-74389G was injected intraperitoneally on days 0, 1 and 2 in a dose of 5 mg/kg. The activity of super-oxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GP), malondialdehyde (MDA) content and hydroxyproline content were performed on days 3, 7, 14 and 28 in lung homogenate. Hydroperoxide concentrations were measured in the plasma.
Results. AD administration affected antioxidant defense system in the lungs, promoted lipid peroxidation, and caused pulmonary fibrosis.
Conclusions. The 21-aminosteroid U-74389G significantly inhibited lipid peroxidation and mitigated fibrous changes in rat lungs provoked by AD.
Keywords: amiodarone, U-74389G, antioxidant system, lipid peroxidation.

Г7. Tashev RE, **Stavreva G**, Velikova MS. Subchronic Central Administration of Cannabinoid Ligands Modulates Nociception in Bulbectomized Rats. Folia medica 2019; 61(4): 540-4, DOI: 10.3897/folmed.61.e47957 ISSN 1314–2143 (online) | ISSN 0204–8043 (print) **SJR 0.311, Q3**

Abstract
Introduction: Endocannabinoid system is involved in neuropsychiatric disorders such as major depression. The bilaterally olfactory bulbectomized rat is widely used as an animal model of depression. The removal of the olfactory bulbs produces behavioural, physiological, and neurochemical alterations resembling clinical depression. There is increasing evidence that highlights the important role of cannabinoid signalling in depression and nociception.
Aim: To investigate the effect of CB1 receptor agonist HU 210 and CB1 receptor antagonist SR 141716A administered icv subchronically (for 7 days) on nociception of rats with model of depression - bilateral olfactory bulbectomy (OBX).
Material and methods: Experimental model of depression - bilateral olfactory bulbectomy (OBX). Bilaterally olfactory bulbectomized rats were used as an experimental model of depression. HU 210 (5 μg) or SR 141716A (3 μg) were infused icv for 7 consecutive days, starting 15 days after the olfactory bulbectomy. Nociception was examined by applying paw pressure test (analgesy-meter) evaluating the rat pain threshold. On day 7, five minutes after the last microinjection, the rats were tested in an analgesy-meter and their mechanically evoked pain responses were measured in arbitrary units (AU).
Results: Microinjections of HU 210 (5 μg) significantly decreased the pain threshold in olfactory bulbectomized rats, while SR 141716A (3 μg) exerted antinociceptive effect by increasing the pain threshold.
Conclusions: Data point to an involvement of CB1 receptors in depression-like behaviour and nociception in olfactory bulbectomized rats and support the data for the association between depressive disorder and pain pathways.
Key words: CB1 cannabinoid receptors, depression, nociception, olfactory bulbectomy, rat

Г8. Himcheva I, Angelova N, Naydenova E, **Stavreva G,** Krastev D, Kochev D, Bocheva A. Synthesis of novel nociceptin analogues: involvement in analgesic effects of opioid and nitric oxideergic systems after cold stress. Journal of Chemical Technology

and Metallurgy, 2021, 56(5): 901-906; ISSN: 1314-7471, **SJR 0.253, Q3**

Abstract
Stressis known to exert an influence on neuroendocrine, autonomic, hormonal, and immune functioning. Various stress models have been reported to induce analgesia. This is a phenomenon, referred to as stress-induced analgesia. Nociceptin and analogues are neuropeptides, neuromodulators, which are able to inhibit the expression of some forms of SIA. Nociceptin/Orphanin FQ(N/OFQ) is a heptadecapeptide which has been found to play a direct role on pain perception. Nitric oxide (NO) plays an important role in initiation and maintenance of pain. It is also known that acute and chronic stresses induce biochemical changes affecting both pain threshold and behaviour. Thus, endogenous opioid peptides and NO, mediated a wide variety of physiological processes including pain transmission and SIA. The aim of the present study was to investigate the effects of novel analogues of N/OFQ(1-13)NH2 , where Lysine (Lys) at position 9 and/or 13 was substituted by L-ornithine (Orn) on nociception after cold stress and the involvement of the opioid and nitric oxideergic systems in these effects. Analgesic activity was examined by nociceptive test - pawpressure (PP). All novel analogues of N/OFQ were injected at a dose of 10 μg kg-1; naloxone (Nal,1 mg kg-1), JTC801 (NOP receptor antagonist, 0,5 mg kg-1), NG-nitro-L-arginine methylester (L-NAME, 10 mg kg-1) and L-arginine (L-Arg, 1mg kg-1). All drugs were dissolved in saline and were injected intraperitoneally (i.p.). The nociceptive tests were performed 10 min after peptide injection. Antinociceptive effects were statistically accessed by ANOVA. In conclusion we suggest that in analgesic effects of the novel analogues of nociceptin were involved opioid-, nociceptin- and nitric- oxideergic systems after cold stress.
Keywords: nociceptin, analogues, stress, naloxone, JTC-801, nitric oxide.

Г9. Himcheva I, **Stavreva G**, Naydenova E, Bocheva A. Involvement of the opioidergic and nociceptinergic systems in the analgetic effect of novel nociceptin analogues after acute and chronic immobilization stress. Pharmacia. 2022;69(4):935-42. DOI 10.3897/pharmacia.69.e89379; ISSN: 0428-0296 **SJR 0.212, Q2**

Abstract
Stress is known to exert an influence on neuroendocrine, autonomic, hormonal functioning. Various stress models have been reported to induce analgesia. This is a phenomenon, referred to as stress-induced analgesia (SIA). Nociceptin/Orphanin FQ(N/OFQ) is a heptadecapeptide that has been found to play a direct role on pain perception. This study aimed to investigate the effects of novel nociceptin analogues on nociception after acute and chronic immobilization stress (CIS) and the involvement of the opioid and nociceptinergic systems in analgesic effects. Analgesic effects were examined by paw-pressure (PP) and hot-plate (HP) tests. Our data showed that acute immobilization stress induced hypoalgesia. The analgesic effect was more pronounced in pain caused by a mechanical stimulus than by a thermal one. CIS attenuated the hyperalgesic effect of naloxone and JTC-801 for mechanical and thermal stimulation. The effects of the opioid system are more pronounced in acute immobilization stress, while the nociceptin mechanisms predominate after chronic stress.
Keywords JTC-801, immobilization stress, naloxone, nociceptin analogues

Г10. Krastev P, Blazhev A, **Stavreva G.** Effect of aminosteroid U74389G in a model of inflammatory bowel disease in rats. J Biomed Clin Res. 2021;14(2):131-139. doi.org/10.2478/jbcr-2021-0018; ISSN:1313-9053 (НАЦИД)

Summary
Lazaroid U-74389G is a synthetic 21-aminosteroid with free radical-scavenging and anti-

inflammatory effects. This study was designed to evaluate the anti-inflammatory activity of U-74389G on experimental 2,4-dinitrobenzene sulfonic acid hydrate (DNBS)-induced colitis in Wistar rats. Five experimental groups were formed: a sham control group, a control group, treated with 0.25 ml of 50% ethanol intrarectally (n=8), a group treated with DNBS (30 mg in 0.25 ml of 50% ethanol administered intrarectally, (n=8), a group treated with DNBS and U-74389G at a daily dose of 15 mg/kg i.p. (n=8), and a group treated with DNBS and sulfasalazine, orally, at a dose of 300 mg/kg. During the experiment, the bodyweight of the rats, food intake, stool consistency, and presence of blood in the stool were recorded as markers of clinical condition. On day 6, colonic tissues were excised and scored for macroscopic and histological damage. Blood samples were taken to measure levels of cytokines by ELISA methods. DNBS decreased significantly body weight (from 237.00±2.52 g to 212.50±6.25 g, p=0.04). The rats treated with U-74389G showed greater food intake and weight gain. U-74389G reduced ulceration index: the U-74389G score was 1.25±0.25, and the DNBS score – 3.87±0.61; p $p<0.05$. All other macroscopic parameters assessed were significantly improved in rats treated with U-74389G. The levels of inflammatory cytokines IL-1, IL6, and TNF-α, were significantly lower than those of the DNBS group, while U-74389G significantly elevated the level of anti-inflammatory IL-10. These findings indicate that U-74389G significantly inhibits colonic inflammatory damages in a rat model of inflammatory bowel disease.

Keywords: cytokines, experimental colitis, inflammatory bowel disease, lazaroid U-74389G

Г11. Komsa-Penkova R, **Stavreva G**, K Belemezova K, Kyurkchiev S, Todinova S, Altankov G. Mesenchymal Stem-Cell Remodeling of Adsorbed Type-I Collagen - Effect of Collagen Oxidation. Int. J. Mol. Sci. 2022;23(6):3058. doi.org/10.3390/ijms23063058; ISSN 1422-0067; **IF 6.208; SJR 1.154. Q1**

Abstract

This study describes the effect of collagen type I (Col I) oxidation on its physiological remodeling by adipose tissue-derived mesenchymal stem cells (ADMSCs), both mechanical and proteolytic, as an in vitro model for the acute oxidative stress that may occur in vivo upon distinct environmental changes. Morphologically, remodeling was interpreted as the mechanical rearrangement of adsorbed FITC-labelled Col I into a fibril-like pattern. This process was strongly abrogated in cells cultured on oxidized Col I albeit without visible changes in cell morphology. Proteolytic activity was quantified utilizing fluorescence de-quenching (FRET effect). The presence of ADMSCs caused a significant increase in native FITC-Col I fluorescence, which was almost absent in the oxidized samples. Parallel studies in a cell-free system confirmed the enzymatic de-quenching of native FITC-Col I by Clostridial collagenase with statistically significant inhibition occurring in the oxidized samples. Structural changes to the oxidized Col I were further studied by differential scanning calorimetry. In the oxidized samples, an additional endotherm with sustained enthalpy (ΔH) was observed at 33.6 ◦C along with Col I's typical one at 40.5 ◦C. Collectively, these data support that the remodeling of Col I by ADMSCs is altered upon oxidation due to intrinsic changes to the protein's structure, which represents a novel mechanism for the control of stem cell behavior.

Keywords: adipose tissue-derived mesenchymal stem cell; collagen type I; remodeling; oxidation

Г12. Komsa-Penkova R, Stoycheva S, Tonchev P, **Stavreva G**, Todinova S, Georgieva G, Yordanova A, Kyurkchiev S, Altankov G. Morphological and Quantitative Evidence for Altered Mesenchymal Stem Cell Remodeling of Collagen in an Oxidative Environment - Peculiar Effect of Epigallocatechin-3-Gallate. Polymers 2022;**14**(19):*3957*. doi.org/10.3390/polym14193957; ISSN 2073-4360; **IF 4.967, SJR 0.72, Q1**

Abstract

Mesenchymal stem cells (MSCs) are involved in the process of extracellular matrix (ECM) remodeling where collagens play a pivotal role. We recently demonstrated that the remodeling of adsorbed collagen type I might be disordered upon oxidation following its fate in the presence of human adipose-derived MSC (ADMSCs). With the present study we intended to learn more about the effect of polyphenolic antioxidant Epigallocatechin-3-gallate (EGCG), attempting to mimic the conditions of oxidative stress in vivo and its putative prevention by antioxidants. Collagen Type I was isolated from mouse tail tendon (MTC) and labelled with FITC before being oxidized according to Fe2+/H2O2 protocol. FITC-collagen remodeling by ADMSC was assessed morphologically before and after EGCG pretreatment and confirmed via detailed morphometric analysis measuring the anisotropy index (AI) and fluorescence intensity (FI) in selected regions of interest (ROI), namely: outside the cells, over the cells, and central (nuclear/perinuclear) region, whereas the pericellular proteolytic activity was measured by de-quenching fluorescent collagen probes (FRET effect). Here we provide morphological evidence that MTC undergoes significant reorganization by the adhering ADMSC and is accompanied by a substantial activation of pericellular proteolysis, and further confirm that both processes are suppressed upon collagen oxidation. An important observation was that this abrogated remodeling cannot be prevented by the EGCG pretreatment. Conversely, the detailed morphometric analysis showed that oxidized FITC-collagen tends to accumulate beneath cells and around cell nuclei, suggesting the activation of alternative routes for its removal, such as internalization and/or transcytosis. Morphometric analysis also revealed that both processes are supported by EGCG pretreatment.

Keywords: adipose tissue-derived mesenchymal stem cell; ADMSC; collagen type I; EGCG; oxidation; remodeling

Г13. Himcheva I, Stavreva G, Naydenova E, Bocheva A. Study of effects of newly synthesised nociceptin analogues on the endocannabinoid system and pain after chronic immobilization stress. Journal of Chemical Technology & Metallurgy. 2023 May 1;58(3). ISSN: 1314-7471, **SJR 0.196, Q3**

Abstract

Stress provokes stress-induced analgesia (SIA), which depends on an opioid and non-opioid components. The non-opioid one comprises several systems among which are endocannabinoid (ECS), adrenergic, and nitricoxidergic participating in the descending antinociceptive system of the body. The ECS system has a well-established role in the modulation of pain perception and behavioral responses after stress. Nociceptin/Orphanin FQ(N/OFQ) is a heptadecapeptide that has been found to play a role in pain perception. This study aimed to investigate the effects of novel nociceptin N/OFQ(1-13)NH2 analogues on nociception after chronic immobilization stress (CIS) and the involvement of the ECS in analgesic effects. The experiments were carried out on male Wistar rats. The animals were immobilized in a tube for 3 hours daily for 4 days. Analgesic effects were examined by the paw-pressure (PP) test. All novel analogues of N/OFQ(1-13)NH2 , the cannabinoid receptor type 1 (CB1-receptor) agonist N-arachidonoylethanolamide (AEA), and the CB1-receptors antagonist N-(Piperidin-1-yl)-5-(4-iodophenyl)-1- (2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (AM251) were administered intraperitoneally (i.p) dissolved in

Dimethyl sulfoxide (DMSO). Statistical analysis was performed using one-way ANOVA. The results showed that nociceptin and analogues administered after CIS decreased the pain threshold significantly compared to a group that underwent chronic stress only. The administration of AEA immediately after the end of stress led to a significantly increased pain threshold, while administration of AM251 significantly decreased the pain threshold versus the both control and group that underwent chronic stress only. Nociceptin and analogues co-administered with CB1-receptor agonist (AEA) or antagonist (AM251) after the end of stress decreased immobilization SIA. Our study gives us reason to assume the participation of ECS in the analgesic effects of the novel nociceptin analogues after chronic immobilization stress.

Keywords: nociceptin analogues, endocannabinoid system (ECS), pain, chronic stress

Г14. Dimitrov B, Georgieva G, Gospodinova K, Tonchev P, Gospodinov D, **Stavreva G**, Komsa-Penkova R. Platelet polymorphism rs5918T > C in the integrin B3 gene modulates comorbidities in patients with psoriasis. Biotechnology & Biotechnological Equipment. 2023;37(1): 2212083. DOI: 10.1080/13102818.2023.2212083 ISSN 13102818, 13143530; **IF 1.762, SJR 0.317; Q3**

Abstract

Psoriasis Vulgaris is a complex multifactorial dermatological disease, with various genetic and environmental factors implicated in the onset and progression of the disease and comorbidities. Cardiovascular disease (CVD) and metabolic syndrome are essential psoriasis comorbidities that suggest a potential hypercoagulable background of the disease. To better understand the link between psoriasis, hypercoagulation and comorbidities, we investigated the prothrombotic polymorphism rs5918T>C in integrin B3 (ITGB3) in 102 patients diagnosed with psoriasis and 97 healthy controls, all Caucasian. The patients, carriers of rs5918T>C polymorphism, were compared with non-carriers for metabolic risk factors related to metabolic syndrome and CV disease. Our results revealed that the incidence of ITGB3rs5918(C) allele carriage was only slightly increased in psoriatic patients compared to healthy controls (20.6% vs 18.6%), and psoriatic patients with the polymorphism showed an increased incidence of metabolic risk factors. Dyslipidemia, high triglycerides (42.9% vs 27.5%), high cholesterol (66.7% vs 45.5%) and low High Density Lipoprotein (HDL) (47.6% vs 32.8%) were significantly more prevalent (p=.019) among psoriatic carriers of the rs5918(C) polymorphism compared to psoriatic non-carriers. The incidence of metabolic syndrome was significantly higher among polymorphism carriers (52.4%) compared to non-carriers (20.5%) within the psoriatic patient group (p=.014), whereas CVD incidence was higher but non-significantly. The carriage of ITGB3rs5918(C) polymorphism in patients with psoriasis was associated with a higher risk of metabolic syndrome and dyslipidaemias and a higher but non-significant prevalence of CVD compared to non-carriers. However, the frequency of this polymorphism was similar in psoriasis patients and healthy controls.

Keywords Psoriasis; metabolic syndrome; cardiovascular disease; ITGB3 rs5918T>C; polymorphism

Г15. Krastev P, Trifonov R, **Stavreva G**. Anti-inflammatory effect of monoammonium glycyrrhizinate on experimental colitis. J Biomen Clin Res. 2023 ISSN:1313-9053 (НАЦИД) (In press) In press

Abstract

Monoammonium glycyrrhizinate (MAG), as a derivative of glycyrrhizic acid has anti-inflammatory, anti-allergic, anti-tumor, antimicrobial, antioxidant, anti-diabetic, anti-ulcer, and hepatoprotective effects. In this study, we aimed to investigate the anti-inflammatory activity of MAG on hapten-

induced experimental colitis induced. MAG in doses 30 and 50 mg/kg was injected intraperitoneally for 6 days, starting one day before inducing colitis with 2,4-dinitrobenzene sulfonic acid. On day 6 colon segments were scored for macroscopic and histological damage. Blood samples were taken to measure levels of cytokines by ELISA methods. Our data showed that MAG at a dose of 50 mg/kg improved clinical symptoms and macroscopic and histological damage of the colon in all the rats with colitis. MAG significantly affected the serum concentrations of inflammatory cytokines TNF-α, IL-1, IL-6, and the level of anti-inflammatory cytokine IL-10 on day 6 after induction of colitis.

These findings indicate that MAG significantly inhibits colonic inflammatory damage in a rat model of inflammatory bowel disease.

Keywords: inflammatory bowel diseases, experimental colitis, monoammonium glycyrrhizinate

Г16.Terziev L, Shopova V, Dancheva V, **Stavreva G**, Atanasova M, Stoyanova A, Lukanov T, Dimitrova A. Influence of MnTE-2-PyP on Inflammation and Lipid Peroxidation in Mouse Asthma Model. Open Journal of Respiratory Diseases, 2012, 2, 37-42. DOI: 10.4236/ojrd.2012.22006; ISSN Online 2163-9418

Abstract

Our aim was to investigate the effects of MnTE-2-PyP on some markers of inflammation and lipid peroxidation in mouse asthma model. 24 female mice were divided into four groups: group 1, controls; group 2, injected with ovalbumin (OVA); group 3, treated with MnTE-2-PyP; and group 4, treated with ovalbumin and MnTE-2-PyP. The mice from groups 2 and 4 were injected with 10 μg OVA and 1 mg Imject Alum® in 100 μL phosphate buffered saline (PBS) on days 0 and 14. The animals from groups 1 and 3 were injected with 100 μL PBS + Imject Alum® (1:1). The animals from groups 2 and 4 were subjected to a 30 min aerosol challenge of 1% ovalbumin on days 24, 25 and 26 and those from groups 1 and 3 were subjected to aerosol challenge of PBS at the same time and duration. One hour before inhalation, and 12 hours later the animals from groups 3 and 4 were injected with 100 μL MnTE-2-PyP solution in PBS containing 5 mg/kg. The total cell number, total protein content and 8-isoprostane, IL-4 and IL-5 levels in the bronchialveolar lavage fluid increased in group 2 as compared to the control group. Malone dialdehyde content in the lung homogenate and IgE levels in the serum also increased in this group. The total cell number, total protein content, and levels of 8-isoprostane, IL-4, IL-5 and IgE decreased significantly in group 4 as compared to the OVA group. The parameters set out above in group 3 did not differ significantly from those of the control group. MnTE-2-PyP administered intraperitoneally, 48 hours after the last nebulization, reduced the inflammation and lipid peroxidation in mouse asthma model.

Keywords: Asthma; Inflammation; Interleukins; 8-Isoprostane; Lipid Peroxidation; MnTE-2-PyP

Г17. **Stavreva G**, Nedialkova N, Negrev N, Radomirov R. Coordination and efficacy of longitudinal and circular muscle in ascending and descending colonic motor activity in a rat model. In A. Y. Kaptanoglu editor. A current perspective on health sciences. Bucuresti: Trakia University; 2014 p. 130-140

Abstract

Aim: To study coordinated movements of longitudinal and circular muscle layers in isolated rat colonic segmrnts.

Materials and methods: Partitioned three-compartment organ bath, electrical field stimulation and mechanographic on-line techniques were used to evaluate spontaneous and electrically-elicited local, ascending and descending motor responses of longitudinal and circular muscles in a rat colonic segments.

Results: The spontaneous motility of isolated colonic segments was characterized by highamplitude irregular contractions of longitudinal and circular muscles, more pronounce in longitudinal layer. The local electrically-induced contractile responses of longitudinal muscle were similar in proximal and distal part of colonic segments. The local responses of circular muscle in proximal or distal part consisted of an initial short relaxation followed by a contraction. The amplitudes of ascending responses of longitudinal muscle (13.2±1.4 mN) exceeded those of circular muscle (4.5±0.7 mN; n=10; $p<0.05$). The descending motor responses of longitudinal muscle were contractions (7.0±0.8 mN) while the descending motor responses of circular muscle consisted by an initial relaxation (-2.3±0.3 mN) followed by a contraction (7.0±0.8 mN). Conclusion: Electrical stimulation co-activates excitatory reflex pathways serving coordinated ascending contractile motor responses of both muscles and descending pathways underlying contraction in longitudinal muscle and relaxation in circular muscle.

Keywords: circular muscle, longitudinal muscle, reflex motor response

Г18. Химчева Ив, **Ставрева Г**, Ангелова Н, Найденова Е, Кръстев Д, Кочев Д, Бочева А. Участие на опиоидергичната система в аналгетичните ефекти на новосинтезирани ноцицептинови аналози при имобилизационен стрес. Здраве и Наука. 2020; брой 1-2, стр.41-44. ISSN 1314-3360

Резюме

Стресът предизвиква стрес-индуцирана аналгезия (СИА), която има опиоидна и неопиоидна компоненти. В неопиоидната са включени различни системи, участващи в низходящата антиноцицептивна система. Целта на изследването беше изучаване ролята на опиоидната система в аналгетичните ефекти на два новосинтезирани N-модифицирани ноцицептинови аналози N/OFQ(1-13)NH_2 – [Orn^9,Orn^{13}] N/OFQ(1-13)NH_2 [Orn^9] N/OFQ(1-13)NH_2 след имобилизационен стрес. Получените резултати показаха, че налоксонът – антагонист на опиоидните рецетори въведен сам понижава болковия праг при животните скед имобилизационен стрес Съвместното въвеждане на налоксана с пептидите също понижи аналгезията след имобилизационен стрес.

Ключови думи: опиоидна система, имобилизационен стрес, ноцицептинови аналози.

Г19. Химчева Ив, **Ставрева Г**, Симеонова Т, Ангелова Н, Найденова Е, Кръстев Д, Кочев Д, Бочева А. Ефекти на ноцицептин и аналози върху болковата перцепция след топлинен стрес при плъхове. Здраве и Наука. 2020; брой 1-2, стр.36-40. ISSN 1314-336

Резюме

Аналгезията, индуцирана от стрес се наблюдава при много видове животни и може да бъде предизвикана от различни стресори – имобилизация, ниска, висока температура, социални стресори. Имобилиционният, студов и топлинен стрес увеличават антиноцицепцията при tail-flick, hot-plate и формалинов тест. Известно е, че стресът предизвиква стрес-индуцирана аналгезия (СИА), която има опиоидан и неопиодна компоненти. Опиоидната компонента е чуствителна към малоксон и налтрексон. При топлинен стрес е застъпена опиоидната компонента, при студов стрес предимно неопиодната, а при имобилизационен и двете компоненти равностойно.

Ключови думи: Опиоидна система, топлинен стрес, ноципептинови аналози

Г20. **Ставрева Г.** Избор на възпроизводим и подходящ модел на експериментален колит. [Reproducibility and suitability of dnbs-induced

experimental colitis.] Сборник доклади. Осемнадесета национална научна сесия за студенти и преподаватели. 29 октомври 2020, гр. Плевен, стр. 146-54. ISBN-978-954-756-248-6

Summary
The aim of this study was to assess the reproducibility and suitability of the experimental colitis, depending upon 2,4-dinitrobenzenesulfonic acid(DNBS) dose. Wistar rats were treated with 10, 20 or 30 mg DNBS. On day 6 colonic tissues were scored for macroscopic and histological damages. Blood samples were taken to measure levels of cytokines by ELISA methods.Score, showing macroscopic damages was significantly higher in DNBS 30 group. Without ulcerations were 38% of rats treated with both lower DNBS doses. The levels of IL-1, IL-6 and TNF-alpha were significantly higher, while the level of IL-10 was decreasedin DNBS 30 group.
Keywords: 2,4-dinitrobenzenesulfonic acid, cytokines, experimental colitis

Г21. Данчева В, Ставрева Г, Терзиев Л, Василева Р. Пневмотоксичен ефект на паракват дихлорид в експериментален модел у плъхове. Сборник доклади от юбилейна научна конференция с международно участие „Нови подходи в общественото здраве и здравната политика“ Плевен, 26 – 28 ноември 2020 г. стр. 84-7 ISBN - 978-954-756-254-7

Summary
Introduction: Paraquat dichloride is bipyridyl pesticide, widely used in agriculture. Pulmonary toxicity of the herbicide is associated with its accumulation in type I and type II pneumocytes and also by provoking oxidative stress in the organism. Aim: The aim of our study was to investigate the influence of paraquat on biochemical markers responsible for toxic pulmonary lesions in rat bronchoalveolar lavage fluid (BALF).
Material and methods: The study was carried out on 64 male Wistar rats (weight 200-250g), divided into two treatment groups: group I, controls; group II, treated with paraquat, solely, administered per os at a dose of 40 mg/kg body weight. Enzyme activities of lactate dehydrogenase (LDH), alkaline phosphatase (AP), acid phosphatase (AcP) and total protein content in BALF were investigated on days 1, 5, 15 and 28 after paraquat treatment.
Results: Isolated administration of paraquat significantly increased the activities of LDH and AcP on days 1 and 5 and the AP activity on day 15 to the control groups. Total protein content in BALF increased sharply (227.4%) on day 1 in the paraquat treated group.
Conclusion: Increased activities of the investigated biochemical markers in BALF confirm the pneumotoxic effect of paraquat through increased cell permeability, destructive changes in pneumocytes and proliferation of type II pneumocytes in rat lung tissue.
Key words: paraquat dichloride, BALF, pneumotoxicity

Г22. Химчева Ив, **Ставрева Г**, Григорян А, Димитрова А, Бочева А. Участие на нитрикоксайдергичната система в аналгетичните ефекти на новосинтезирани ноцицептинови аналози след хроничен имобилизационен стрес. Варненски медицински форум. 2021;10(3):50-54. ISSN: 1314-8338

Резюме
Стресът е сред причините за редица нервно-психични заболявания. При стрес в резултат от сложното взаимодействие между ендокринната, имунната и централната нервна система се наблюдават функционални и структурни промени в организма. Променят се болковата перцепция и поведенческите отговори. Аналгезията, индуцирана от стрес, може да бъде предизвикана от различни стресори. Стресът предизвиква стрес-индуцираната аналгезия

(СИА). Ноцицептин/орфанин FQ (N/OFQ) е невропептид със 17-аминокиселинна последователност, който повлиява ноцицепцията. Ноцицептин и аналозите са невропептиди, невромодулатори, които намаляват различните форми на стрес-индуцираната аналгезия. Азотният оксид (NO) има важна роля в болковата перцепция. Известно е, че повлиява ноцицепцията при остър и хроничен стрес. Следователно, опиоидните невропептиди и NO медират ноцицепцията и СИА. Целта на изследването беше изучаване участието на нитрикоксайдергичната система в аналгетичните ефекти на нови N-модифицирани ноцицептинови аналози N/OFQ(1-13)NH2 -[Orn9 ,Orn13]N/OFQ(1-13)NH2 и [Orn9]N/OFQ(1-13) NH2 след хроничен имобилизационен стрес. Експериментите бяха проведени върху мъжки плъхове, порода Wistar (180-200 g), със свободен достъп на вода и храна, при температура 22 ± 2.0 C. Промените в болковата активност бе оценена с прилагане на механично дразнене - paw pressure (PP) тест. Изследваните субстанции бяха въвеждани интраперитонеално (i.p.). Ноцицептин и аналозите бяха инжектирани в доза 10 μg/kg, L-NAME - 10 mg/kg и L-arginine (L-arg) - 1mg/kg, 10 мин след имобилизационния хроничен стрес. Контролната група бе инжектирана с физиологичен разтвор в обем 0,1 ml/kg (i.p.). Експерименталните данни бяха обработени статистически чрез ANOVA. Получените резултати показаха, че в аналгетичните ефекти на новите ноцицептинови аналози участва азотноокисната невротрансмитерна система след хроничен имобилизационен стрес.

Ключови думи: ноцицептин и аналози, хроничен имобилизационен стрес, L-arginine, L-NAME, ноцицепция

Г23. Кръстев П, Кръстева Г, Цолова Е, Цанкова В, Динков Б, Тотева Г, **Ставрева Г.** Ефект на моноамониев глициризинат върху експериментален колит при плъхове. Сборник статии от IIIта национална научна конференция „Дръзновение и младост във фармакологията" , 30 септември – 02 октомври 2022 г., Цигов чарк. 86-93. ISBN 978-619-237-120-3

Summary

Monoammonium glycyrrhizinate (MAG) acts as a free radical-scavenging an antioxidant, hepatoprotective, antiulcer, anti-inflammatory agent. We evaluated the anti-inflammatory activity of MAG on experimental 2,4- dinitrobenzenesulfonic acid hydrate (DNBS)-induced colitis in Wistar rats. The experiment was carried out in 5 groups: a sham control group; a control group treated with 0.25 ml of 50% ethanol intrarectally; treated with DNBS 30 mg in 0.25 ml of 50% ethanol administered intrarectally; treated with DNBS and MAG at a daily dose of 50 mg/kg intraperitoneally; treated with DNBS and sulfasalazine, orally, at a dose of 300 mg/kg. The body weight of the rats, food intake, stool consistency, and presence of blood in the stool was recorded as markers of clinical condition. On day 6 colon segments were scored for macroscopic and histological damage. Blood samples were taken to measure levels of cytokines by ELISA methods. DNBS decreased significantly body weight (from 237.00±2.52 g to 212.50±6.25 g, p=0.04). Rats treated with MAG showed greater food intake and weight gain. MAGreduced ulceration index: MAGscore was 1.25±0.25 and DNBS score – 3.87±0.61; p<0.05. All other assessed macroscopic parameters were significantly improved in rats treated with MAG. The levels of inflammatory cytokines IL-1, IL-6, and TNF-α were significantly lower than those of the DNBS group, while the level of antiinflammatory IL-10 was significantly elevated by U-74389G. These findings indicate that MAG inhibits significantly colonic inflammatory damages in a rat model of inflammatory bowel disease.

Keywords: MAG, cytokines, experimental colitis, inflammatory bowel disease.

Г24. Валентинова Ц, Димитров Д, Ставрева Г, Вълкова С, Тончев П. Маринов Х.

Възможности за използване на дигитални технологии в традиционното обучение по медицина и здравни грижи. Сборник доклади Национална научно-практическа конференция “Дигитална трансформация на образованието – проблеми и решения, оценяване и акредитация”, Русенски университет, 198-202. ISBN 978-954-712-892-7

Abstract

Opportunities for using the digital technologies in traditional education for medicine and health care Tsvetelina Valentinova, Dobromir Dimitrov, Galia Stavreva, Sonia Valkova, Pencho Tonchev, Hristo Marinov Abstract: The coronavirus pandemic forced, in a short period of time, the training in all specialties taught at the Medical University-Pleven to be implemented in a distance format. After resumption of attendance an extensive survey was conducted among 830 students from all specialties of the university to investigate their satisfaction with online learning. Students noted some advantages of distance learning, but also indicated a range of weaknesses, mainly related to the implementation of the practical part of training in medical specialties. In this context, according to the specifics of the medical education, MU-Pleven emphasizes on the implementation of the new digital technologies added to traditional medical training such as: 3D medical table for virtual dissections, a virtual reality studio with 360-degree view of the operating room, 3D studio for live surgery demonstrations, a training studio with holographic images, augmented reality studio, resuscitation center and telepathology, 3D printing and bioprinting laboratories.

Keywords: digital technologies, medical education