EFFECTS OF SELENIUM SUPPLEMENTATION ON LIPID PEROXIDATION AND SERUM ANTIBODIES AGAINST ADVANCED GLYCATION END PRODUCTS IN SPONTANEOUSLY HYPERTENSIVE RATS

Boryana Ruseva, Miglena Georgieva, Milena Atanasova, Margarita Alexandrova, Pavlina Laleva

Faculty of Medicine

Medical University – Pleven

Bulgaria

Key words: selenium, SHR, lipid peroxidation products, anti-AGEs antibodies

Abbreviations:

AGEs - advanced glycation end products

Anti- AGEs abs - antibodies against advanced glycation end products

GPx-1 - Glutathione peroxidase 1

ROS - reactive oxygen species

Se - selenium

SHR - spontaneously hypertensive rats

Correspondence address: Boryana Ruseva, MD, assistant professor

Department of physiology, Medical University of Pleven

1, "St. Kliment Ohridski" str., 5800 Pleven, Bulgaria

e - mail: ruseva.bk@mail.bg

Mobile phone: +359 887364704

SUMMARY

Advanced glycation end products have been implicated in the pathogenesis of many disorders, such as diabetes, hypertension, and aging. Excessive accumulation of these products has been shown to lead to tissue damage (alteration of tissue proteins structure and function, stimulation of cellular responses through specific receptors or generation of reactive oxygen species). On the other hand, considerable evidence suggests that oxidative stress accelerates formation of advanced glycation end products. The aim of the present study was to investigate the effects of selenium supplementation on lipid peroxidation and the serum level of antibodies against advanced glycation end products in spontaneously hypertensive rats. Sixteen male, 8 months old SHR were divided into 2 groups: the first group received a dietary selenium supplementation for 8 weeks and the second group was fed in an adequate selenium content diet. The selenium nutritional status was assessed by measuring GPx -1 activity in whole blood, using “Ransel” kit of “Randox Laboratories LTD”. The serum lipid hydroperoxide concentration was evaluated by the method of Yagi.The serum level of antibodies against advanced glycation end products was determined by the method of indirect ELISA. The results showed an increased GPx -1 activity in whole blood in first group as compared to second group (p=0,02), while the lipid hydroperoxide concentration and serum level of antibodies against advanced glycation end products were significantly reduced in the selenium supplemented SHR. Selenium supplementation reduces oxidative stress and serum level of antibodies against advanced glycation end products in SHR.

Key words: selenium, SHR, lipid peroxidation products, antibodies against advanced glycation end products

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MEDECINE

Médecine expérimentale

STRAIN-DEPENDENT RESPONSES TO BRAIN OXIDATIVE STRESS AND ARTERIAL BLOOD PRESSURE IN NORMOTENSIVE AND SPONTANEOUSLY HYPERTENSIVE RATS. EFFECTS OF LOSARTAN

Milena Atanasova, Anelia Dimitrova*, Daniela Pechlivanova, Jana Tchekalarova****

(*Submitted by Corresponding Member R. Radomirov on November 11, 2010*)

Abstract

Experimental data suggest that oxidative stress is involved in hypertension. The aim of this study was to evaluate and compare the effect of chronic systematic treatment with AT1 receptor antagonist losartan on arterial blood pressure and the production of oxidative damage in the brain of normotensive Wistar and spontaneously hypertensive rats (SHRs). Drug administration was conducted via subcutaneous osmotic minipumps for 14 days (10 mg/kg per day). Spontaneously hypertensive rats showed an increase in the arterial blood pressure compared to normotensive Wistar rats. Long-term losartan exposure attenuated hypertension in SHRs. The level of lipid peroxidation was higher in both the frontal cortex and the hippocampus of SHRs compared to Wistar rats. However, chronic block of AT1 receptors decreased the level of lipid peroxidation of the above mentioned brain structures in Wistar and SHRs. Losartan influenced positively the citosolic superoxide dismutase (SOD/CuZn) activity in both the frontal cortex and the hippocampus of SHRs while it enhanced the activity of this antioxidant enzyme only in the hyppocampus of Wistar rats. No changes in the mitochondrial SOD/Mn activity in both the frontal cortex and the hippocampus were detected after losartan treatment in Wistar and SHRs. These data suggest that the strain differences of the level of oxidative stress in the frontal cortex and the hippocampus as well as arterial blood pressure determine different responses after long-term infusion with AT1 receptor antagonist.

Key words: losartan, Wistar, spontaneously hypertensive rat, arterial blood pressure, oxidative stress

Introduction. In the recent years the crucial role of oxidative stress in the occurrence and the development of hypertension has received an increasing attention. The brain is particularly sensitive to attacks of reactive oxygen

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BIOLOGIE
Physiologie

EFFECTS OF SELENIUM SUPPLEMENTATION ON ANTIBODIES AGAINST ADVANCED GLYCATION END PRODUCTS AND LIPID PEROXIDATION IN YOUNG NORMOTENSIVE AND SPONTANEOUSLY HYPERTENSIVE RATS

Boryana Ruseva, Milena Atanasova*, Margarita Alexandrova, Pavlina Laleva***, Anelia Dimitrova*****

(*Submitted by Corresponding Member R. Radomirov on December 20, 2011*)

Abstract

Advanced glycation end products (AGEs) have been implicated in the pathogenesis of many disorders. Excessive accumulation of AGEs has been shown to lead to tissue damage through a variety of mechanisms including alteration of tissue protein structure and function, or increased generation of reactive oxygen species. On the other hand, oxidative stress accelerates AGEs formation. Selenium (Se) is an exogenous antioxidant which performs its biological role via selenoprotein expression.

The aim of this study was to investigate the effect of selenium (Se) on the serum level of antibodies against AGEs (anti-AGEs abs) and lipid peroxidation in young normotensive Wistar (WKY) and spontaneously hypertensive (SHR) rats.

Fifteen male WKY and twenty male SHR, 16 weeks old, divided into 4 groups, were tested after being on a Se-adequate diet (NSe) or a Se-supplemented diet (HSe) for eight weeks. The Se nutritional status was assessed by measuring Glutathione peroxidase (GPx-1) activity in whole blood, using "Ransel" kit of Randox Laboratories LTD. The serum anti-AGEs abs level was determined by the method of indirect ELISA. The serum lipid hydroperoxide concentration (ROOH) was evaluated by the method of Yagi.

The results showed that Se supplementation increased GPx-1 activity of whole blood of the rats ($p < 0.05$). The serum anti-AGEs abs and ROOH levels of SHR NSe were higher than those detected in WKY NSe, and they were significantly reduced in the SHR HSe ($p < 0.05$).

In conclusion, selenium supplementation reduces oxidative stress and serum anti-AGEs abs level in SHR.

Key words: selenium, rats, anti-AGEs antibodies, lipid peroxidation products

Original Research

Effects of selenium on the vessel walls and anti-elastin antibodies in spontaneously hypertensive rats

Boryana Ruseva[1], Milena Atanasova[2], Miglena Georgieva[2], Nikolay Shumkov[3] and Pavlina Laleva[4]

[1]Department of Physiology; [2]Department of Biology, Medical University, Pleven 5800; [3]National Center of Public Health Protection, Sofia 1431; [4]Central Clinical Laboratory of University Hospital, Pleven 5800, Bulgaria
Corresponding author: Boryana Ruseva, Department of Physiology, Medical University – Pleven, 1, 'Kliment Ohridski' Street, Pleven 5800, Bulgaria. Email: ruseva.bk@mail.bg

Abstract

Selenium (Se) is an exogenous antioxidant that performs its role via expression of selenoproteins. Pathological changes of the structure of the vessel wall, elastin turnover and collagen production may lead to increased stiffness of the vessels with decreased blood flow to the peripheries. The level of anti-elastin antibodies (AEABs) may give information for elastin metabolism. The aim of the study is to investigate the influence of Se intake on the vessel wall changes and production of AEABs in spontaneously hypertensive rats (SHR). Twenty-four male, 32-week-old SHR were used, divided into three groups, G1, G2 and G3. Before blood and morphological testing, G1 received a low-Se diet for eight weeks, G2 received a diet with adequate Se content and G3 received a diet with Se supplementation. The Se nutritional status was assessed by determination of glutathione peroxidase-1 (GPx-1) activity in whole blood, using the 'Ransel' kit. The rats from group G3 showed higher GPx-1 activity and lower level of AEABs than the other groups ($P = 0.021$), and the aortic wall histology showed slight degenerative changes compared with other rats. A low-Se diet caused severe changes to the aortic wall's ultrastructure, whereas Se supplementation slowed the changes down. The morphometry revealed a thicker abdominal aortic wall in rats of G1 compared with the other groups, and reduced thickness of the wall of the left coronary artery in G3 compared with the other groups ($P < 0.05$). Our results have shown that low Se intake leads to severe changes in the vessel walls in SHR, whereas selenium supplementation slows down the elastin degradation and degenerative changes of the vessel walls.

Keywords: selenium, GPx-1 activity, SHR, vessel wall, anti-elastin antibodies

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Introduction

It is considered that the physiological effects of selenium (Se) are due mainly through the functions of selenoproteins (enzymes that incorporate Se in the form of one or more selenocysteine residues) as their expression are controlled by 25 selenoprotein genes.[1] Tissue expression of these enzymes depends on the daily Se intake, which occurs mainly by food. It has been established that for normal growth and reproduction in mammals, a diet containing 0.1 μg Se/g of food is enough.[2–4] Se-dependent cellular glutathione peroxidase-1 (GPx-1) is the most abundant intracellular isoform of the GPx antioxidant enzyme family, and it plays a major role in the control of reactive oxygen species (ROS), which participate in atherogenesis and in the pathogenesis of hypertension. As continuously exposed to a blood flow, endothelial cells are the primary target of an oxidant-induced injury.[5,6] Many studies are focused on the role of trace elements for normal endothelial function, but there is not enough evidence about their effect on the metabolism of the proteins of the underlying connective-tissue matrix. Elastin is the main component of the vessel wall. Pathological changes in elastin turnover and increased production of collagen may lead to a disturbance of the vessel's structure, increasing the stiffness of the vessel walls and decreasing blood supply to the organs. Autoantibodies to α-elastin (an elastin breakdown product) and tropoelastin (an elastin precursor) are found in the serum of healthy human individuals and correlate with their respective serum peptide concentrations.[7,8] They are considered as physiological autoantibodies and are assumed to be a part of a homeostatic mechanism,

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Strain-dependent effects of long-term treatment with melatonin on kainic acid-induced status epilepticus, oxidative stress and the expression of heat shock proteins

Milena Atanasova [a], Zlatina Petkova [b], Daniela Pechlivanova [b], Petya Dragomirova [a], Alexander Blazhev [a], Jana Tchekalarova [b,*]

[a] Department of Biology, Medical University of Pleven, 1 Kliment Ohridski Str., Pleven 5800, Bulgaria
[b] Institute of Neurobiology, Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Bl. 23, Sofia 1113, Bulgaria

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ABSTRACT

Oxidative stress is implicated in the pathogenesis of both hypertension and epileptogenesis, therefore it could be used as a tool for studying co-morbidity of hypertension and epilepsy. Clinical data suggest that melatonin is a potent antioxidant that is effective in the adjunctive therapy of hypertension and neurodegenerative diseases. The present study aimed to explore and compare the efficacy of chronic pretreatment with melatonin infused via subcutaneous osmotic mini-pumps for 14 days (10 mg/kg per day) on kainic acid (KA)-induced status epilepticus, oxidative stress and expression of heat shock protein (HSP) 72 in spontaneously hypertensive rats (SHRs) and normotensive Wistar rats. SHRs showed higher lipid peroxidation (LP) in the frontal cortex and hippocampus and decreased cytosolic superoxide dismutase (SOD/CuZn) production in the frontal cortex compared to Wistar rats. Status epilepticus (SE) induced by KA (12 mg/kg, i.p.) was accompanied by increased LP and expression of HSP 72 in the hippocampus of the two strains and increased SOD/CuZn production in the frontal cortex of SHRs. Melatonin failed to suppress seizure incidence and intensity though the latency for seizure onset was significantly increased in SHRs. Melatonin attenuated the KA-induced increase in the level of LP in the hippocampus both in SHRs and Wistar rats. However, an increased activity in SOD/CuZn and mitochondrial SOD Mn as well as reduced expression of HSP 72 in the hippocampus was observed only in Wistar rats pretreated with melatonin. Taken together, the observed strain differences in the efficacy of chronic melatonin exposure before SE suggest a lack of a direct link between the seizure activity and the markers of oxidative stress and neurotoxicity.

1. Introduction

Epilepsy has been described as a condition of excessive neuronal discharge associated with or resulting from oxidative stress (Shin et al., 2011; Waldbaum and Patel, 2010). Epileptic biomarkers, such as catalytical antioxidants and oxidative products in neuronal tissues have been monitored for evaluation of the degree of epileptic pathogenesis. The neurotoxin kainic acid (KA) triggers neuropathologic cellular changes in the hippocampus characterized by an overloading of intracellular calcium, mitochondrial membrane rupturing, activation of intracellular enzyme cascades, including the nitric oxide synthase and increased levels of free radicals/reactive oxygen species (ROS) from the mitochondrial intermembrane space into the cytosol (Srivastava et al., 2008). The formation of free radicals results in an extensive lipid peroxidation (LP), which damages cellular organelles and membranes, and finally leads to cell death. Thus, oxidative stress resulting from excitotoxicity is suggested to play a critical role in epileptic brain damage (Bondy and Lee, 1993). Harmful changes in cells, including calcium influx and generation of ROS induce or suppress the expression of genes in neurons thereby influencing synthesis of proteins (Rajdev and Sharp, 2000). The expression of stress proteins, referred to members of heat shock proteins (HSP) is caused by a variety of injurious stimuli in the brain and is also considered as an appropriate marker of excitoxicity. Several studies suggested that there exists a close relationship between ROS and the expression of members of the HSP 70 family (Ambrosio et al., 1995; Kukreja et al., 2002; Lee and Corry, 1998). In addition, the increased expression of HSP 70 was seen after KA-induced SE in rat brain (Gupta and Briyal, 2006).

The disturbance in the levels of the antioxidant enzymes is a crucial step involved in dysregulation of physiological processes implicated in the pathogenesis of arterial hypertension (Harris, 1992). Experimental data demonstrate that the direction of changes in the activity of

Abbreviations: KA, kainic acid; HSP, heat shock protein; SHRs, spontaneously hypertensive rats; SE, status epilepticus; LP, lipid peroxidation; SOD/CuZn, cytosolic superoxide dismutase; ROS, reactive oxygen species.

* Corresponding author. Tel.: +359 887267052.
E-mail address: janetchekalarova@gmail.com (J. Tchekalarova).

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ORIGINAL RESEARCH

Strain-Dependent Effects of Sub-chronically Infused Losartan Against Kainic Acid-Induced Seizures, Oxidative Stress, and Heat Shock Protein 72 Expression

Jane Tchekalarova · Natasha Ivanova · Daniela Pechlivanova · Kalina Ilieva · Milena Atanasova

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Abstract We studied the involvement of angiotensin (Ang) II AT_1 receptors in the pathophysiology of kainate (KA)-induced neurotoxicity, focusing on the regulation of the oxidative stress state and expression of HSP 72 in the frontal cortex and hippocampus in two strains, spontaneously hypertensive rats (SHRs) and normotensive Wistar rats. The KA injection was executed after the rats were infused subcutaneously via osmotic mini-pumps with losartan (10 mg/kg day) for 14 days. Losartan delayed the onset of KA-induced seizures in SHRs but not in Wistar rats without affecting the seizure intensity score. This selective AT_1 receptor antagonist decreased the lipid peroxidation only in naive SHRs. However, it attenuated the KA-induced increase in lipid peroxidation in both SHRs and Wistar rats. The adaptive enhancement of cytosolic superoxide dismutase (SOD) activity in KA-treated SHRs was recovered to control level after sub-chronic losartan infusion while no change in mitochondrial SOD activity was detected in the two strains. Both losartan and KA produced a higher expression of HSP 72 in the hippocampus of the two strains compared to naive rats infused with vehicle. Taken together, our findings demonstrate that the efficacy of a sub-chronic systemic losartan infusion in preventing the KA-induced seizure activity and neurotoxicity is more pronounced in SHRs, considered as a model of essential hypertension, than in normotenisve Wistar rats. The results suggest that the blockade of AT1 receptors, commonly used as a strategy for prevention of high blood pressure, may be useful as an adjunctive treatment in status epilepticus to reduce oxidative stress and neurotoxicity.

Keywords Kainic acid · Losartan · Oxidative stress · Heat shock protein 72 · Spontaneously hypertensive rats · Wistar rats

J. Tchekalarova (✉) · N. Ivanova · D. Pechlivanova
Institute of Neurobiology, Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Bl. 23, Sofia 1113, Bulgaria
e-mail: janetchekalarova@gmail.com

K. Ilieva · M. Atanasova
Department of Biology, Medical University of Pleven, 1 Kliment Ohridski Str., Pleven 5800, Bulgaria

Introduction

The brain renin–angiotensin system (RAS) is involved in the regulation of classic physiology and behaviors including blood pressure, sodium and body water balance, pituitary gland hormones, and reproductive hormones, as well as thirst-related and sexual behaviors. Most of these functions are mediated through the AT_1 receptor subtype activation (Wright et al. 2008). The non-peptide and selective AT_1 receptor antagonist losartan is routinely used for studying the functions of the biologically active brain neuropeptide angiotensin (Ang) II and the role of AT_1 receptor subtype, in particular. There is growing literature data suggesting that Ang peptides mediate brain excitability, including seizure susceptibility. Thus, the Ang II-induced inhibition of hippocampal and gyrus dentatus long-term potentiation (LTP) is prevented by co-injection with losartan suggesting that this effect was mediated via activation of the AT_1 receptor subtype (Armstrong et al. 1996a, b; Denny et al. 1991; Wayner et al. 1993, 1995). The Ang II suppressed the NMDA- and/or kainate (KA)-evoked increase in the discharge rate of dorsal lateral geniculate nucleus probably mediated by AT_1 receptors (Albrecht et al. 1997). The above-mentioned Ang II effects on some electrophysiological parameters are in accordance with our previous pharmacological results on animal

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Abnormal levels of serum anti-elastin antibodies in patients with symptomatic carotid stenosis

Plamen Tzvetanov[a], Vish Hegde[a], Jasem Y. Al-Hashel[c], Milena Atanasova[b], Aman P.S. Sohal[a], Rossen T. Rousseff[c,*]

[a] Department of Neurosciences, University Hospitals, Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK
[b] Department of Biology, Medical University of Pleven, Kliment Ohridski st 1, Pleven 5800, Bulgaria
[c] Department of Neurology, Ibn-Sina Hospital, pob 25427, Safat 13115, Kuwait

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ABSTRACT

Background and objective A correlation between the levels of antibodies to alpha-elastin (alpha-AEAb) and tropoelastin (tropo-AEAb) and the corresponding peptide concentration is found in human serum in health and disease. Serum elastin peptide and anti-elastin antibodies (AEAb) levels are age-related and vary with the stages of atherosclerotic vascular damage. This study aims to determine if elastin metabolism (assessed by the ratio of tropo-AEAb to alpha-AEAb) differs in patients with symptomatic carotid stenosis versus subjects with asymptomatic stenosis.
Patients and methods: Alpha-AEAb and tropo-AEAb were measured by ELISA in blood sera of 65 patients with ultrasound verified high-grade symptomatic carotid stenosis (resulting in stroke 1–7 days before measurement) compared to 51 patients with asymptomatic stenosis.
Results: Serum anti-alpha-elastin IgG levels are extremely increased in symptomatic versus asymptomatic carotid stenosis. The ratio of tropo-AEAb (reflecting elastin synthesis) to alpha-AEAb (a function of elastin degradation) was 3.7 in symptomatic stenosis versus 14.2 in asymptomatic stenosis ($p < 0.001$).
Conclusions: There is a significant difference in elastin metabolism in patients with symptomatic carotid stenosis versus asymptomatic stenosis. The ratio of tropo-AEAb to alpha-AEAb as an index of elastin synthesis/degradation proves useful in investigation of atherosclerotic lesions and may represent a new immunologic marker for carotid plaque destabilization.

1. Introduction

Elastin is a major component of the extracellular matrix. Changes of its metabolism are involved in pathophysiology of destructive lesions of elastin-rich organs, such as blood vessels, kidney, skin and lungs. Elevation of serum elastin-derived peptides (EDPs) levels is observed in emphysema, abdominal aortic aneurysm and atherosclerosis [1–3].

Mature atherosclerotic lesions develop a fibrous cap composed of dense extracellular matrix containing collagen and elastin. Degradation of elastin in arterial walls is a characteristic feature of atherogenesis [4,5]. The products of degradation are EDPs that have been detected and quantified in circulating blood [3,6]. Their serum levels are increased only in ulcerative, but not in occlusive atherosclerotic lesions [3].

Serum EDPs are immunogenic and provoke the synthesis of anti-elastin antibodies (AEAbs) [6]. These secondary immune and inflammatory responses to elastin might lead to further elastinolysis and production of more EDPs triggering a vicious circle which causes further degradation of the fibrous cap [4,5].

We undertook this study in an attempt to compare elastin turnover in stroke patients with symptomatic carotid stenosis (resulting in stroke 1–7 days before measurement) versus subjects with asymptomatic stenosis. We measured the absolute levels of serum tropo-AEAb (that correlates with elastin synthesis) and alpha-AEAb (that parallels with elastin degradation) and used the ratio of tropo-AEAb to alpha-AEAb as an index of elastin metabolism.

2. Patients and methods

2.1. Patients

The study enrolled 116 patients (mean age: 62.5; SD: 11.3; range: 28–85 years; 53 women) with ultrasound verified internal carotid stenosis as a part of research project. The study procedures are approved by a Local Ethic Committee. All the patients

* Corresponding author. Tel.: +96566379970; fax: +96524948226/96524849226.
E-mail address: rossentrousseff@yahoo.co.uk (R.T. Rousseff).

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Effect of *Aronia melanocarpa* fruit juice on amiodarone-induced pneumotoxicity in rats

Stefka Valcheva-Kuzmanova, Galya Stavreva[1], Violeta Dancheva[2], Ljudmil Terziev[3], Milena Atanasova[4], Angelina Stoyanova[5], Anelia Dimitrova[6], Veneta Shopova[2]

Department of Preclinical and Clinical Pharmacology and Toxicology, Medical University, Varna, [1]Department of Experimental and Clinical Pharmacology, Medical University, Pleven, [2]Department of Disaster Medicine, Medical University, Pleven, [3]Department of Clinical Laboratory, Clinical Immunologyand Allergology, Clinic of Allergology, University Hospital, Pleven, [4]Departments of Biology, [5]Chemistry, and [6]Physiology and Pathophysiology, Medical University, Pleven, Bulgaria

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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

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INTRODUCTION

Amiodarone (AD), an iodine-containing highly lipophilic benzofuran derivative, is a very effective class III, long-acting antiarrhythmic drug. It causes acute pneumonitis resulting in fatal pulmonary fibrosis.[1] *In vivo* and *in vitro* studies have shown that AD is directly toxic to lung cells[2] such as alveolar macrophages,[3] alveolar epithelial cells,[4] and pulmonary artery endothelial cells.[5] AD and its primary metabolite N-desethylamiodarone have been demonstrated to cause apoptosis and necrosis in cultured alveolar type II cells.[4] AD-induced pulmonary injury could include disruption of mitochondrial function and cellular adenosine triphosphate ATP levels,[6] enhanced oxidative stress and increased production of reactive oxygen species,[7,8] activation of alveolar macrophages and cytokine release.[9-11]

Aronia melanocarpa (Michx.) Elliot (black chokeberry) originates from the eastern parts of North America and East Canada. Its migration to Europe and the former Soviet Union occurred around 1900. *Aronia* is commonly used to produce fruit syrup, juice, jellies, tea, and wine. Chokeberry fruits are extremely rich in phenolic compounds: Procyanidins, flavonoids (mainly from the subclass of anthocyanins) and phenolic acids.[12] A series of studies has investigated the antioxidant properties of *Aronia* juice, *Aronia* extract or its phenolic constituents using different well-established assays.[12-18] Fresh *Aronia* berries possess the highest antioxidant capacity among berries and other fruits investigated so far as measured with oxygen radical absorbance capacity.[13,15] Studies have demonstrated that flavonoids including anthocyanins possess anti-inflammatory activity due to the suppression

Address for correspondence:
Prof. Stefka Valcheva-Kuzmanova, Department of Preclinical and Clinical Pharmacology and Toxicology, Medical University, 55, Marin Drinov Str.,9002 Varna, Bulgaria.
E-mail: stefkavk@yahoo.com

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MEDECINE
Pathophysiologie

CHANGES IN THE SERUM LEVELS OF ENDOTHELIN-1, MATRIX METALLOPROTEINASES-2, -9 AND C-REACTIVE PROTEIN IN PATIENTS WITH MILD AND SEVERE DEGREE OF ARTERIAL HYPERTENSION

Krasimir Kostov, Anelia Dimitrova, Armine Grigoryan, Snejana Tisheva*, Adelaida Ruseva, Milena Atanasova***, Constantin Gospodinov*, Alexander Blazhev*****

(*Submitted by Corresponding Member R. Radomirov on October 21, 2013*)

Abstract

Haemodynamic stress in arterial hypertension leads to increased production of endothelin-1 (ET-1). Changes in the extracellular matrix are controlled largely by methalloproteinase-2 (MMP-2) and methalloproteinase-9 (MMP-9) which play an important role in vascular remodelling of hypertension. C-reactive protein (CRP) is an acute phase protein which is synthesized by hepatocytes under the effect of interleukin-6 (IL-6) in inflammation.

The purpose of the study was to investigate the relationship of ET-1, MMP-2, MMP-9 and CRP with the degree of arterial hypertension and the systemic and vascular inflammatory response.

Three groups were formed: group I – 31 patients with mild hypertension (MH); group II – 29 patients with severe hypertension (SH); group III – 15 persons in a control group (CG). ET-1 was determined by ELISA kit of "Biomedika", MMP-2 and MMP-9 by ELISA kit of the "R&D Systems", and the CRP – through immunoturbidimetric method with monoclonal anti-CRP antibodies. The analysis used the statistical program STATGRAPHICS.

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Physiologie

EFFECTS OF PINEALECTOMY ON ANXIETY AND DEPRESSIVE-LIKE BEHAVIOUR IN WISTAR RATS

Zlatina Nenchovska, Lidia Kortenska, Miroslava Stefanova, Liana Alova, Milena Atanasova*, Jana Tchekalarova

(*Submitted by Academician P. Vassileva on October 3, 2014*)

Abstract

In the present study, we aimed to investigate the influence of endogenous melatonin abolishment via pinea lectomyone motional behaviour associated with anxiety and depressive responses in male Wistar rats. Sham-operated (sham) or pinealectomised (Pin) rats were tested in the hole-board (HB) test, elevated plus maze (EPM), sucrose preference test (SCT) and forced swimming test (FST) one month (Ist trial) and three months (IInd trial) after surgery. Melatonin deficit caused a significant decrease of the head-dipping at the holes accompanied by increased time of stereotype grooming both during the Ist and the IInd trial. Pinealectomy elevated both the number of entries and the time spent on the open arms in EPM test and this effect was significant a month after the removal of the pineal gland. Sucrose preference was decreased in Pin rats compared to sham rats during the light phase in both the Ist and the IInd trial, respectively. The immobility time tested in FS was significantly increased a month after pinealectomy. The observed depressive behaviour in Pin rats was accompanied by a tendency of decreased 5-HT release from the hippocampus. Taken together, a model of melatonin deficit caused an impulsive- and depressive-like behaviour, which was evident three months after pinealectomy. Our results suggest that endogenous melatonin synthetized in the pineal gland affects these behavioural responses through a regulatory mechanism on the hippocampal 5-HT release.

Key words: pinealectomy, anxiety, depression, serotonin

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[Reproductive problems in women with PCOS, the impact of PAI-1 carriers of 4G PAI-1 polymorphism and BMI]

[Article in Bulgarian]

R Komsa-Penkova, G Golemanov, G Georgieva, K Popovski, N Slavov, P Ivanov, K Kovacheva, M Atanasova, A Blajev

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Abstract

Approximately 7-12% of women in reproductive age are affected by PCOS[2] and 40 to 70 percent of them are overweight contributing to the clinical picture of PCOS and increased reproductive and metabolic disorder. In order to investigate the role of PAI-1 as a possible risk factor for the development of PCOS a group of 67 women with polycystic ovarian disease and 70 healthy controls were investigated for levels of PAI-1 and carriage of the promoter polymorphism 675 4G/5G in gene of PAI-1. The correlation with BMI was checked. The results of the DNA analysis showed a high carriage of polymorphism 675 4G/4G in promoter of PAI-1 gene in women with PCOS but not significant (OR = 1.655; p = 0.141), as well in the total group of the patient (OR =1.474; p>0.05). Serum levels of PAI-1 were significantly higher in total group of patients compared to controls. The levels of PAI-1 is correlated with carriage of 675 4G/5G polymorphism in the gene for PAI-1 (r=0.534; p=0.03) as well as with BMI, like correlation coefficients were higherin the group with PCOS (0.572; p=0.04). Data from the disease history showed a higher percentage of women with reproductive problems: early pregnancy loss 48.5% and infertility 23.2%, significantly higher in the group with PCOS (58.1% compared to 32.4%). The carriers of polymorphism 4G are at greater risk for early pregnancy loss than those with 5G (61.45% as compared to 36.8%), which confirms that carriage of the polymorphism 4G/5G 675 gene PAI-1 has a specific in multifactorial pathogenesis and expression of PCOS.

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Research Article

Effect of Selenium Supplementation on Redox Status of the Aortic Wall in Young Spontaneously Hypertensive Rats

Boryana Ruseva,[1] Milena Atanasova,[2] Reni Tsvetkova,[3] Tatyana Betova,[3] Margarita Mollova,[4] Margarita Alexandrova,[5] Pavlina Laleva,[6] and Aneliya Dimitrova[7]

[1]*Department of Physiology, Medical University, 1 Kliment Ohridski, 5800 Pleven, Bulgaria*
[2]*Department of Biology, Medical University, 1 Kliment Ohridski, 5800 Pleven, Bulgaria*
[3]*Department of Common and Clinical Pathology, Medical University, 1 Kliment Ohridski, 5800 Pleven, Bulgaria*
[4]*Institute of Biology and Immunology of Reproduction, Bulgarian Academy of Sciences, 73 Tsarigradsko Shose, 1113 Sofia, Bulgaria*
[5]*Department of Biophysics, Medical University, 1 Kliment Ohridski, 5800 Pleven, Bulgaria*
[6]*Central Clinical Laboratory of University Hospital, 8 Georgi Kochev, 5800 Pleven, Bulgaria*
[7]*Department of Pathological Physiology, Medical University, 1 Kliment Ohridski, 5800 Pleven, Bulgaria*

Correspondence should be addressed to Boryana Ruseva; ruseva.bk@mail.bg

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Selenium (Se) is an exogenous antioxidant that performs its function via the expression of selenoproteins. The aim of this study was to explore the effect of varying Se intake on the redox status of the aortic wall in young spontaneously hypertensive rats (SHR). Sixteen male Wistar Kyoto (WKY) rats and nineteen male SHR, 16-week-old, were tested after being given diets with different Se content for eight weeks. They were divided into 4 groups: control groups of WKY NSe and SHR NSe on an adequate Se diet and groups of WKY HSe and SHR HSe that received Se supplementation. The Se nutritional status was assessed by measuring whole blood glutathione peroxidase-1 (GPx-1) activity. Serum concentration of lipid hydroperoxides and serum level of antibodies against advanced glycation end products (anti-AGEs abs) were determined. Expression of GPx-1 and endothelial nitric oxide synthase (eNOS) were examined in aortic wall. Se supplementation significantly increased GPx-1 activity of whole blood and in the aortas of WKY and SHR. Decreased lipid peroxidation level, eNOS-3 expression in the aortic wall, and serum level of anti-AGEs abs were found in SHR HSe compared with SHR NSe. In conclusion, Se supplementation improved the redox status of the aortic wall in young SHR.

1. Introduction

Recent years have witnessed an increased interest in the role of free radical processes in physiology and pathophysiology of the organism. A greater understanding of the mechanisms of production and elimination of reactive oxygen species (ROS) and identification of factors that control or modulate them may help develop relevant strategies for prevention and treatment of ROS-mediated disease states.

Many scientists have been considering the possibility of modulating the progression of hypertension by using antihypertensive drugs and diets within the specific life stages when the organism is most sensitive to endogenous and exogenous factors. Genetically determined hypertension of spontaneously hypertensive rats (SHR) could be used as a model for investigations of the period of life when temporary treatment with adequate drugs or diets may prevent a cardiovascular system from developing pathological changes. Prepubertal and pubertal periods (the age between 4th and 10th weeks of life) are the appropriate periods for the short treatment of SHR by antihypertensive drugs and diets, because at this time intervention is able to have a long-term effect on the development of the cardiovascular system and on the reorganization of hemodynamics [1].

The endothelium is a dynamic structure that has a main importance for maintenance of normal function of cardiovascular system, because of release of vasoactive substances. It is evaluated that abnormal redox state of an arterial wall

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Abnormally high levels of anti-collagen type IV IgG antibodies in the serum of patients with a clinically isolated syndrome correlate with an increased risk of conversion to MS

Behidhe Sadarzanska-Terzieva[a,*], Plamen Tzvetanov[b], Vishwajit Hegde[c], Jasem Y. Al-Hashel[d], Rossen T. Rousseff[d], Lubomir Haralanov[e], Boyko Stamenov[a], Milena Atanassova[f], Iveta Marinova[g], Anna Marinova[g], Adelaida Rousseva[h]

[a] Department of Neurology and Neurosurgery, University Hospital of Pleven, Georgi Kochev st 8A, Pleven 5800, Bulgaria
[b] Department of Clinical Neurophysiology, Sandringham level 1, Leicester Royal Infirmary, University Hospital of Leicester, Leicester LE1 5WW, UK
[c] Department of Neurosciences, University Hospital of Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK
[d] Department of Neurology, Ibn-Sina Hospital, Kuwait, POB 25427, Safat 13115, Kuwait
[e] National Hospital in Cardiology, Neurology Clinic, 65 Konjovitsa Str., Sofia 1309, Bulgaria
[f] Department of Biology, Medical University of Pleven, Kliment Ohridski St. 1, Pleven 5800, Bulgaria
[g] Department of Psychology, Affiliate "Prof Ivan Mitev" of Vratza, Medical University of Sofia, School Complex 1, Vratza 3000, Bulgaria
[h] Department of Clinical Laboratory, University Hospital of Pleven, Georgi Kochev St. 8A, Pleven 5800, Bulgaria

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ABSTRACT

Objective: To investigate anti-collagen-type-IV serum antibodies (ACIVAbs) levels in patients with clinically isolated syndrome (CIS), and to determine their predictive value for conversion into multiple sclerosis (MS).
Material and Methods: Serum levels of IgM and IgG ACIVAbs in 40 untreated patients with CIS (13 male, mean age 34.85 ± 11.4 years, range 16–58 years) were compared to those of 27 gender- and age-matched healthy controls. ACIVAbs were quantified using ELISA. Patients were followed for 5 years by clinical examination and MRI studies.
Results: Thirty two patients (80%) converted to MS (converted CIS, C-CIS group) while the rest 8 (20%) did not (non-converted CIS, NC-CIS). The C-CIS patients had significantly higher levels of IgG ACIVAb compared to NC-CIS while the IgM levels did not differ between C-CIS and NC-CIS. Conversion to MS occurred in 66% of patients with IgG ACIVAbs levels exceeding the 95th percentile found in controls. IgG ACIVAbs levels correlated positively with the serum levels of matrix metalloproteinases type 9 ($r = 0.37$; $p = 0.003$) and inversely with those of tissue inhibitor of metalloproteinases type 1 ($r = -0.43$; $p = 0.0008$).
Conclusion: High serum levels of IgG ACIVAbs in patients with CIS correlate strongly with increased risk of conversion to MS.

1. Introduction

Predicting the risk of conversion of clinically isolated syndrome (CIS) into definitive multiple sclerosis (MS) is important in patient management [1–3]. While advances in imaging have contributed to define early treatment strategies, the approach in many cases remains debatable [4–6]. Autoimmune inflammation is cardinal in MS pathogenesis, and therefore, a search for immunological markers for the presence and activity of disease had begun long ago and still continues.

The results concerning the predictive value of individual autoantibodies studied are not very encouraging at this stage [6–9]. The presence of IgG oligoclonal bands in cerebrospinal fluid is a well established and important predictive factor for conversion [4,10], but the role of autoantibodies against synthesized N-glycosylated peptides [11], anti-alpha-glucose-based glycan [12], myelin basic protein, and myelin oligodendrocyte protein [13], remains inconclusive.

Collagen type IV is a principal constituent of brain–blood barrier and inflammatory disruption of the blood–brain barrier is a major mechanism in MS [1]. We, therefore, decided to assess the levels

* Corresponding author. Tel.: +359 64 80 22 46; fax: +359 64 80 22 46.
E-mail address: tzvetanovplamen@hotmail.com (B. Sadarzanska-Terzieva).

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Research report

Consequences of long-term treatment with agomelatine on depressive-like behavior and neurobiological abnormalities in pinealectomized rats

Jana Tchekalarova[a,*], Zlatina Nenchovska[a], Dimitrina Atanasova[a], Milena Atanasova[b], Lidia Kortenska[a], Miroslava Stefanova[a], Liana Alova[a], Nikolai Lazarov[c]

[a] Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia, Bulgaria
[b] Department of Biology, Medical University of Pleven, 1 Kliment Ohridski Str., Pleven 5800, Bulgaria
[c] Department of Anatomy, Medical Faculty, MU-Sofia, Bulgaria

HIGHLIGHTS

- Agomelatine prevented depressive behavior in pinealectomized rats.
- Agomelatine attenuated enhanced hippocampal 5-HT release in pinealectomized rats.
- Agomelatine restored the negative feedback inhibition of HPA axis.
- Agomelatine exerted a neuroprotection in pinealectomized rats.

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ABSTRACT

Previous data have shown that the rat model of melatonin deficit can cause a number of neurobiological aberrations. The aim of the present study was to determine whether the antidepressant drug agomelatine, a MT1/MT2 melatoninergic receptor agonist/5-HT2C receptor antagonist is able to prevent some of the behavioral, biochemical and cellular abnormalities induced by pinealectomy. The injection of agomelatine (40 mg/kg, i.p. for 5 weeks)/vehicle started after pinealectomy/sham procedure in Wistar rats. Animals were tested in different behavioral tests for anxiety and depression during the period of agomelatine treatment (chronic effect) and two months later (plastic effect). The effect of agomelatine on KCl-evoked serotonin (5-HT) release from the hippocampus, the activity of the hypothalamic–pituitary–adrenal (HPA) axis and neuronal loss in pinealectomized rats were assessed. Our results showed that agomelatine not only did not prevent the disturbed emotional arousal/anxiety behavior in pinealectomized rats during the treatment but the enhanced motor activity and decreased anxiety state was still observed two months after the discontinuation of treatment. However, the drug corrected a depressive-like behavior (chronic and plastic effect), alleviated the enhanced KCl-evoked 5-HT release in the hippocampus, recovered the suppressed negative feedback inhibition of HPA axis and exerted a neuroprotection in pinealectomized rats. Our findings suggest that pinealectomy can model melancholic depression disorder while the antidepressant action of agomelatine is associated with a correction of 5-HT release in the hippocampus, dysregulated HPA system and neuroprotection in limbic structures.

1. Introduction

Although the exact role of melatonin in pathogenesis of depression is uncertain, studies have reported decreased nocturnal and phase-shifted melatonin levels both in animal models and patients with depression [1–4]. A deficiency of melatonin is suggested to underlie the predisposition to melancholic depression characterized by psychopatological and neurobiological disturbances, including agitation, anhedonia, circadian fluctuation of mood, disturbance in sleep physiology, weight loss, increase in plasma cortisol and monoamine oxidase activity [5–7].

* Corresponding author at: Institute of Neurobiology, Acad. G. Bonchev Str Bl. 23, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria.
E-mail address: janetchekalarova@gmail.com (J. Tchekalarova).

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Article

Serum Concentrations of Endothelin-1 and Matrix Metalloproteinases-2, -9 in Pre-Hypertensive and Hypertensive Patients with Type 2 Diabetes

Krasimir Kostov [1,*], Alexander Blazhev [2], Milena Atanasova [2] and Anelia Dimitrova [1]

[1] Department of Physiology and Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; anelija.dimitrova@gmail.com
[2] Division of Biology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; yalishanda9@gmail.com (A.B.); milenaar2001@yahoo.com (M.A.)
* Correspondence: dr.krasi_kostov@abv.bg; Tel.: +359-889-257-459

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Abstract: Endothelin-1 (ET-1) is one of the most potent vasoconstrictors known to date. While its plasma or serum concentrations are elevated in some forms of experimental and human hypertension, this is not a consistent finding in all forms of hypertension. Matrix metalloproteinases -2 and -9 (MMP-2 and MMP-9), which degrade collagen type IV of the vascular basement membrane, are responsible for vascular remodeling, inflammation, and atherosclerotic complications, including in type 2 diabetes (T2D). In our study, we compared concentrations of ET-1, MMP-2, and MMP-9 in pre-hypertensive (PHTN) and hypertensive (HTN) T2D patients with those of healthy normotensive controls (N). ET-1, MMP-2, and MMP-9 were measured by ELISA. Concentrations of ET-1 in PHTN and N were very similar, while those in HTN were significantly higher. Concentrations of MMP-2 and MMP-9 in PHTN and HTN were also significantly higher compared to N. An interesting result in our study is that concentrations of MMP-2 and MMP-9 in HTN were lower compared to PHTN. In conclusion, we showed that increased production of ET-1 in patients with T2D can lead to long-lasting increases in blood pressure (BP) and clinical manifestation of hypertension. We also demonstrated that increased levels of MMP-2 and MMP-9 in pre-hypertensive and hypertensive patients with T2D mainly reflect the early vascular changes in extracellular matrix (ECM) turnover.

Keywords: pre-hypertension; type 2 diabetes; endothelin-1; matrix metalloproteinases-2; matrix metalloproteinases-9; vascular remodeling

1. Introduction

Endothelin-1 is one of the most potent vasoconstrictors known in humans to date [1]. Although, different types of cells, including cardiac myocytes, vascular smooth muscle cells (VSMCs), fibroblasts, or epithelial cells are able to synthesize and release ET-1, the most important biological source is the vascular endothelium [2]. ET-1 is secreted primarily from the endothelial cells and influenced of the underlying VSMCs. Considering that approximately 80% of the total amount of ET-1 synthesized by endothelial cells is released toward the basolateral side of cells, tissue levels are higher than plasma levels. Thus, ET-1 acts primarily as a paracrine/autocrine peptide, and not as a circulating hormone [3]. Except through impact on vascular tone, ET-1 is involved in the complex regulation of BP through effects on renal hemodynamics and water-salt balance, influence on adrenal aldosterone, and catecholamine production, it also participates in the central and baroreceptor regulation and has positive inotropic effects on the heart [4]. In addition, ET-1 potentiates the action of other vasoconstrictors, such as angiotensin II (Ang II), phenylephrine, and serotonin [5].

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Chronic Treatment with Minoxidil Induces Elastic Fiber Neosynthesis and Functional Improvement in the Aorta of Aged Mice

Marion Coquand-Gandit[1], Marie-Paule Jacob[2], Wassim Fhayli[1345], Beatriz Romero[6], Miglena Georgieva[7], Stéphanie Bouillot[18], Eric Estève[1345], Jean-Pierre Andrieu[9], Sandrine Brasseur[345], Sophie Bouyon[345], Natalio Garcia-Honduvilla[6], Philippe Huber[18], Julia Buján[6], Milena Atanasova[7], Gilles Faury[1345]
Affiliations expand

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Abstract

Normal arterial aging processes involve vascular cell dysfunction associated with wall stiffening, the latter being due to progressive elastin and elastic fiber degradation, and elastin and collagen cross-linking by advanced glycation end products (AGEs). These processes progressively lead to cardiovascular dysfunction during aging. Elastin is only synthesized during late gestation and childhood, and further degradation occurring throughout adulthood cannot be physiologically compensated by replacement of altered material. However, the ATP-dependent K^+ channel opener minoxidil has been shown to stimulate elastin expression in vitro and in vivo in the aorta of young adult rats. Therefore, we have studied the effect of a 10-week chronic oral treatment with minoxidil (120 mg/L in drinking water) on the aortic structure and function in aged 24-month-old mice. Minoxidil treatment increased tropoelastin, fibulin-5, and lysyl-oxidase messenger RNA levels, reinduced a moderate expression of elastin, and lowered the levels of AGE-related molecules. This was accompanied by the formation of newly synthesized elastic fibers, which had diverse orientations in the wall. A decrease in the glycation capacity of aortic elastin was also produced by minoxidil treatment. The ascending aorta also underwent a minoxidil-induced increase in diameter and decrease in wall thickness, which partly reversed the age-associated thickening and returned the wall thickness value and strain-stress relation closer to those of younger adult animals. In conclusion, our results suggest that minoxidil presents an interesting potential for arterial remodeling in an antiaging perspective, even when treating already aged animals.

Keywords: advanced glycation end products; aging; arteries; elastin; mechanics; minoxidil.

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Research Article

Melatonin modulates inflammatory response and suppresses burn-induced apoptotic injury

Ganka Bekyarova[1], Milena Atanasova[2], Maria Tzaneva[3], Anelia Dimitrova[2]

[1]Medical University-Varna, Department of Pathophysiology, Bulgaria
[2]Medical University- Pleven, Department of Biology, Bulgaria
[3]Medical University-Varna, Department of General and Clinical Pathology, Bulgaria

Abstract

Introduction: Melatonin, the principal secretory product of the pineal gland, has antioxidant functions as a potent antioxidant and free radical scavenger. **Objectives** of the present study were to investigate the effect of melatonin against inflammatory response, burn-induced oxidative damage and apoptotic changes of rat liver. **Methods**: Melatonin (10 mg /kg, i.p.) was applied immediately after 30% of total body surface area (TBSA) burns on male Wistar rats. The level of malondialdehyde (MDA) as a marker of an oxidative stress was quantified by thiobarbituric method. Hepatic TNFα and IL-10 as inflammatory markers were assayed by ELISA. Using light immunochistochemistry the expression Ki67 proliferative marker was investigated. **Results**: Hepatic MDA and TNF-α levels increased significantly following burns without any change in IL-10 level. Intracellular vacuolization, hepatic cell degeneration and apoptosis occurred in rats after burns. The number of apoptotic cells was increased whereas no significant increase in Ki67 proliferative marker. Melatonin decreased the MDA and TNF-α content and increased the IL-10 level. It also limited the degenerative changes and formation of apoptotic cells in rat liver but did not increase expression of the marker of proliferation. **In conclusion**, our data show that melatonin relieves burn-induced hepatic damage associated with modulation of the proinflammatory/anti-inflammatory balance, mitigation of lipid peroxidation and hepatic apoptosis.

Keywords: melatonin, cytokines, lipid peroxidation, apoptosis, liver, burn

✉ Correspondence should be addressed to: Ganka Bekyarova; e-mail: ganka.bekyarova@gmail.com

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Agomelatine protects against neuronal damage without preventing epileptogenesis in the kainate model of temporal lobe epilepsy

Jana Tchekalarova [a,*], Dimitrinka Atanasova [a,b], Zlatina Nenchovska [a], Milena Atanasova [c], Lidia Kortenska [a], Rumyana Gesheva [a], Nikolai Lazarov [a,d]

[a] Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria
[b] Department of Anatomy, Faculty of Medicine, Trakia University, Stara Zagora 6003, Bulgaria
[c] Department of Biology, Medical University of Pleven, Pleven 5800, Bulgaria
[d] Department of Anatomy and Histology, Medical University of Sofia, Sofia 1431, Bulgaria

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ABSTRACT

Recent studies about the novel antidepressant agomelatine, which is a mixed MT_1 and MT_2 melatonin receptor agonist and $5HT_{2C}$ serotonin receptor antagonist possessing an anticonvulsant and neuroprotective action, suggest that it may have potential to contribute against epileptogenesis and epilepsy-induced memory impairment. In order to ascertain whether protection of some brain structures could suppress epileptogenesis, in the present study, we evaluated the effect of chronic post-status treatment with agomelatine on epileptogenesis, behavioral and neuronal damage induced by kainate acid (KA) status epilepticus (SE). Agomelatine/vehicle treatment (40 mg/kg, i.p.) started one hour after SE and continued up to 10 weeks in Wistar rats. Latency for onset of spontaneous motor seizures (SMS) and their frequency was detected by a 24-h video-recording. Locomotor activity, anxiety and hippocampus-dependent spatial memory in open field (OF), elevated plus maze (EPM), light-dark test (LDT) and radial arm maze (RAM) test, respectively, were evaluated during the last two weeks after SE. Agomelatine significantly decreased the latency for onset of SMS and increased the seizure frequency during the 2nd and the 3rd week of treatment. The MT_1 and MT_2 receptor agonist and serotonin $5HT_{2C}$ receptor antagonist exacerbated the KA-induced hyperlocomotion and impulsive behavior and it was unable to prevent spatial memory impairment of epileptic rats. However, agomelatine induced a neuroprotection in the dorsal hippocampus, specifically in the CA1, septal CA2 and partially in the CA3c region, the hilus of the dentate gyrus, piriform cortex and septo-temporal and temporal basolateral amygdala. Our findings suggest that the beneficial impact against SE-induced neuronal loss exerted by agomelatine is not crucial for the suppression of epileptogenesis and its deleterious consequences in KA model of temporal lobe epilepsy.

1. Introduction

Agomelatine, developed by the pharmaceutical company Servier, was introduced as a new class of antidepressants in Europe in 2009. This drug has been actively studied in recent years by many research groups using different experimental models characterized by cellular, neurochemical and behavioral abnormalities (Boulle et al., 2016; Mairesse et al., 2013; Morley-Fletcher et al., 2011; Rainer et al., 2012). Agomelatine became the focus of increased scientific interest due to its unique pharmacological mechanism of action. This compound can exert chronobiotic efficacy because of its agonism on MT_1/MT_2 melatonin receptors while its antidepressant and anxiolytic effect depends on synergistic activation of melatonin receptors and antagonism of 5-HT_{2C} serotonin receptors (Guardiola-Lemaitre et al., 2014; Stahl, 2014). The beneficial effects of agomelatine against depression, anxiety, memory impairment and sleep disorder have been found both in animal models and in patients (reviewed in: Comai and Gobbi, 2014).

Numerous preclinical and clinical studies are in support of the hypothesis that melatonin can be used in seizure control and epilepsy (Bazil et al., 2000; Borowicz et al., 1999; Lapin et al., 1998; Lima et al., 2011; Rufo-Campos, 2002). In line with experimental results, clinical data confirm a potential efficacy of melatonin as a powerful antioxidant to be applied as an add-on option in the treatment of patients with epilepsy (Gupta et al., 2004). It has been suggested that low plasma levels

Abbreviations: KA, kainate acid; SE, status epilepticus; SMS, spontaneous motor seizures; OF, open field; EPM, elevated plus maze; LDT, light-dark test; RAM, radial arm maze test; PTZ, pentylenetetrazol; SHRs, spontaneously hypertensive rats; TLE, temporal lobe epilepsy; PB, phosphate buffer.

* Corresponding author at: Institute of Neurobiology, Acad. G. Bonchev Str., Bl. 23, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria.
E-mail address: janetchekalarova@gmail.com (J. Tchekalarova).

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ORIGINAL STUDY

SERUM CONCENTRATIONS OF MATRIX METALLOPROTEINASE-9, -13 AND TIMP-1 IN AN OVARIECTOMIZED WISTAR RAT MODEL OF OSTEOPOROSIS

Armine V. Grigoryan[1], Anelia A. Dimitrova[1], Krasimir G. Kostov[1], Adelaida L. Ruseva[2], Milena A. Atanasova[3], Alexander B. Blazhev[3], Tatyana M. Betova[4]

[1] Department of Physiology and Pathophysiology, Medical University – Pleven, Bulgaria
[2] Department of Clinical Laboratory, Medical University – Pleven, Bulgaria
[3] Department of Biology, Medical University – Pleven, Bulgaria
[4] Department of Pathoanatomy, Medical University – Pleven, Bulgaria

Abstract

Introduction. Osteoporosis is a disease characterized by decreased bone density and destruction of the microarchitectonics of the bone structure. This leads to increased bone fragility and risk of fracture particularly of the hip, spine, wrist and shoulder. Osteoporosis is known as „The Silent Epidemic of the Century" because bone loss occurs without symptoms. Altered ovarian function is one of the most common causes of osteoporosis. Indicators for altered bone homeostasis are the changes in serum levels of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs).
Objective. The aim of current study was to determine the activity of alkaline phosphatase (ALP) and serum concentrations of MMP-9, MMP-13 and TIMP-1 in the ovariectomized rats.
Materials and Methods. An experiment was performed on 35 female Wistar rats at reproductive age – 2 months divided into 2 groups: group 1 (G1)-20 animals were sham-operated (sham) and group 2 (G2)-15 were ovariectomized (ovx).

Résumé

Concentrations du sérum des métallo-protéinases matricielles-9, –13 et TIMP-1 dans un modèle d'ostéoporose à déficit ostrogénique d'un rat Wistar femelle

Introduction. L'ostéoporose est une maladie caractérisée par une diminution de la densité de la masse osseuse et la destruction de la micro-architecture de la structure osseuse. Cela conduit à une fragilité osseuse accrue et à un risque de fracture, en particulier de la hanche, de la colonne vertébrale, du poignet et de l'épaule. L'ostéoporose est connue comme «l'épidémie silencieuse du siècle» parce que la perte osseuse se produit sans symptômes.L'altération de la fonction ovarienne est l'une des causes les plus fréquentes de l'ostéoporose. Les indicateurs de l'altération de l'homéostasie osseuse sont les changements dans les taux sériques des métallo-protéinases matricielles (MMPs) et de leurs inhibiteurs tissulaires (TIMPs).
Objectifs. Le but de cette étude était de déterminer l'activité de la phosphatase alcaline (ALP) et

Corresponding author: Armine Grigoryan
Department of „Physiology and Pathophysiology", Medical University-Pleven
„Kliment Ohridski" Str., № 1, 5800 Pleven, Bulgaria
e-mail: armine14@abv.bg; phone: 0886-31-99-33

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Chronic agomelatine treatment prevents comorbid depression in the post-status epilepticus model of acquired epilepsy through suppression of inflammatory signaling

Jana Tchekalarova[a,*,1], Dimitrinka Atanasova[a,b,c,1], Lidia Kortenska[a], Milena Atanasova[d], Nikolai Lazarov[a,e]

[a] Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria
[b] Department of Anatomy, Faculty of Medicine, Trakia University, Stara Zagora 6003, Bulgaria
[c] Department of Genes and Behavior, Max Planck Institute of Biophysical Chemistry, Gottingen 37077, Germany
[d] Department of Biology, Medical University of Pleven, Pleven 5800, Bulgaria
[e] Department of Anatomy and Histology, Medical University of Sofia, Sofia 1431, Bulgaria

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Wistar rat

ABSTRACT

Inflammatory signal molecules are suggested to be involved in the mechanism underlying comorbid depression in epilepsy. In the present study, we tested the hypothesis that the novel antidepressant agomelatine, a potent melatonin MT_1 and MT_2 receptor agonist and serotonin $5HT_{2C}$ receptor antagonist, can prevent depressive symptoms developed during the chronic epileptic phase by suppressing an inflammatory response. Chronic treatment with agomelatine (40 mg/kg, i.p.) was initiated an hour after the kainate acid (KA)-induced status epilepticus (SE) and maintained for a period of 10 weeks in Wistar rats. Registration of spontaneous motor seizures was performed through a video (24 h/day) and EEG monitoring. Antidepressant activity of agomelatine was explored in the splash test, sucrose preference test (SPT) and forced swimming test (FST) while anxiolytic effect was observed through the novelty suppression-feeding test (NSFT) during chronic phase in epileptic rats. The frequency of motor seizures detected by video and EEG recording did not differ between vehicle and Ago group. Rats with registered spontaneous motor seizures showed symptoms typical for depressive behavior that included decreased grooming, anhedonia during the dark period and hopeless-like behavior. Epileptic rats exhibited also anxiety with novelty-induced hypophagia. This behavioral deficit correlated with increased signal markers of inflammation (plasma levels of interleukin (IL)-1β and activated glia in brain), while plasma corticosterone levels were not changed. Agomelatine treatment during epileptogenesis exerted a clear antidepressant effect by suppressing all behavioral hallmarks, reducing plasma IL-1β levels and preventing microgliosis and astrogliosis in specific limbic regions. The present results suggest that agomelatine treatment starting after SE can provide an effective therapy of comorbid depression in chronic epileptic condition through suppression of inflammatory signaling.

1. Introduction

Clinical studies showed that depression is the most frequent psychiatric disorder accompanying epilepsy, and, in particular, temporal lobe epilepsy (TLE) (Kanner and Balabanov, 2002; Kondziella et al., 2007). The models of TLE induced by pilocarpine- and kainic acid (KA) in rats are associated with neurochemical (deficit in serotoninergic neurotransmission) and behavioral (anhedonia and despair-like behavior) changes resembling clinical form of depression (Mazarati et al., 2008; Tchekalarova et al., 2011). Inflammation is an important hallmark of both major depression and TLE while cytokines, which participate in neuronal activity, are considered relevant biomarkers of inflammatory response in epilepsy (Perez-Caballero et al., 2014; Vieira et al., 2015). The critical role of inflammation in the brain and periphery during epileptogenesis, and in particular the potential contribution of interleukin (IL)-1β system in the mechanism underlying comorbid depression has been suggested in animal model of TLE (Pineda et al., 2012). Clinical data are also in support of the idea that there is a close link between IL-1β-511T polymorphism and TLE with hippocampal sclerosis (Kanemoto et al., 2003; Kauffman et al., 2008).

* Corresponding author at: Institute of Neurobiology, Acad. G. Bonchev Str., Bl. 23, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria.
E-mail address: janetchekalarova@gmail.com (J. Tchekalarova).
[1] These authors contributed equally to this work.

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Agomelatine treatment corrects symptoms of depression and anxiety by restoring the disrupted melatonin circadian rhythms of rats exposed to chronic constant light

Jana Tchekalarova[a,*], Tzveta Stoynova[a], Kalina Ilieva[b], Rumyana Mitreva[a], Milena Atanasova[b]

[a] Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria
[b] Department of Biology, Medical University of Pleven, Pleven 5800, Bulgaria

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ABSTRACT

Desynchronization of circadian rhythms is a hallmark of depression. The antidepressant agomelatine, which is an MT_1/MT_2 melatonin receptor agonist/5-HT_{2C} serotonin receptor antagonist has advantages compared to the selective serotonin reuptake inhibitors as a circadian phase-shifting agent. The present study was designed to explore whether agomelatine is able to have an antidepressant effect on rats exposed to chronic constant light (CCL) for 6 weeks. Focus is also placed on whether this activity affects diurnal rhythms of depressive-like symptoms and is associated with restoration of impaired circadian rhythms in plasma melatonin and corticosterone. We report that CCL induced a depressive-like symptoms associated with decreased grooming in the splash test during the subjective light/inactive phase. Anhedonia-like deficit in the saccharine preference test and increased immobility in the forced swimming test were both detected during the subjective dark/active phase. The disturbed emotional fluctuations due to CCL were corrected by agomelatine treatment (40 mg/kg, i.p. for 3 weeks). Agomelatine also restored novelty-induced hypophagia, which reflects an anxiety state, during the subjective Light and Dark phase, respectively, in rats exposed to CCL. Parallel to the observed positive influence on behavior, this melatonin analogue restored impaired circadian patterns of plasma melatonin but not that of corticosterone. These findings demonstrated the antidepressant-like effect of agomelatine in rats exposed to CCL possibly exerted via correction of melatonin rhythms and are suggestive of the therapeutic potential of this drug in a subpopulation of people characterized by a melatonin deficit.

1. Introduction

The pineal gland is the main source of circulating plasma melatonin and its rhythmic secretion modulates the circadian dynamics of a number of physiological functions (Reiter et al., 2014). The gland receives neuronal projections from the main biological clock, suprachiasmatic nucleus (SCN). This determines the daily rhythm of hormonal synthesis, secretion and synchronization of physiological parameters with the light/dark cycle. In the recent decades, studies focused on disturbed circadian biological rhythms and the potential of negative consequences have been of significant interest to researchers aiming to discover the mechanisms for a number of pathologies from cells to organism. Experimental studies which explored chronobiotic efficacy of melatonin support the hypothesis that rather than being regulated by light, secretion of this hormone is the main synchronizing signal that coordinates internal physiological functions of the light/dark cycle. Exposure to light at night suppresses melatonin release causing lessening of its synchronizing activity on peripheral cells. Continuous illumination can lead to a number of pathologies in both experimental animals (Brown et al., 1991) and humans (Danilenko et al., 2011), resulting from chronobiological disturbance associated with the inhibition of rhythmic melatonin secretion during the dark period. These pathologies are most commonly associated with depressive symptoms, although the precise mechanisms of the underlying link between depression and circadian rhythms remain uncertain (Kronfeld-Schor and Einat, 2012). It is accepted that circadian rhythms of important physiological and biochemical parameters are impaired in a state of depression (McClung, 2007).

Clinical data demonstrated that patients with depression have fluctuating depressive symptoms, affecting sleep, mood, core temperature and hormone secretion. Circadian rhythms have been found to be phase shifted, diminished in amplitude or out of phase with each other (Quera Salva et al., 2011; Wirz-Justice, 2008). It is accepted that the disturbance in the circadian rhythm of release of important hormones,

* Corresponding author at: Institute of Neurobiology, Acad. G. Bonchev Str., Bl. 23, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria.
E-mail address: janetchekalarova@gmail.com (J. Tchekalarova).

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Anticonvulsant effect of anacardic acid in murine models: Putative role of GABAergic and antioxidant mechanisms

Antonio Luiz Gomes Júnior[a,b,c], Jana Dimitrova Tchekalarova[d], Milena Atanasova[e], Keylla da Conceição Machado[a,b,c], Maria Alexsandra de Sousa Rios[f], Márcia Fernanda Paz Jardim[a,b,c], Mihnea-Alexandru Găman[g,h], Amelia Maria Găman[i,j], Santosh Yele[k], Manik Chandra Shill[l], Ishaq N. Khan[m], Md. Amirul Islam[n], Eunüs S. Ali[o,p,1], Siddhartha K. Mishra[q], Muhammad Torequl Islam[r,s,*], Mohammad S. Mubarak[t,**], Luciano da Silva Lopes[a], Ana Amélia de Carvalho Melo-Cavalcante[b,c]

[a] *Laboratório de Pesquisa em Neuroquímica Experimental do Programa de Pós-graduação em Ciências Farmacêuticas da Universidade Federal do Piauí, CEP: 64.049-550, Teresina, Brazil*
[b] *Laboratório de Toxicidade Genética do Programa de Pós-graduação em Ciências Farmacêuticas da Universidade Federal do Piauí, CEP: 64.049-550, Teresina Brazil*
[c] *Programa de Pós-Graduação em Biotecnologia (RENORBIO) da Universidade Federal do Piauí, Teresina, Brazil*
[d] *Instituto de neurobiologia da Academia de Ciências da Bulgária, Sofia, Bulgaria*
[e] *Departamento de Biologia, Universidade Medica de Pleven, Pleven, Bulgaria*
[f] *Grupo de Inovação Tecnológicas e Especialidades Químicas – GRINTEQUI, Universidade Federal do Ceará, Fortaleza, Brazil*
[g] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[h] *Facoltà di Medicina e Chirurgia, Università degli Studi di Bari "Aldo Moro", Bari, Italy*
[i] *Department of Pathophysiology, Research Center of Experimental and Clinical Medicine, University of Medicine and Pharmacy of Craiova, Romania*
[j] *Department of Haematology, Filantropia City Hospital of Craiova, Craiova, Romania*
[k] *School of Pharmacy and Technology Management, SVKM's NMIMS, Shirpur, India*
[l] *Department of Pharmaceutical Sciences, North South University, Bashundhara, Dhaka, 1229, Bangladesh*
[m] *Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, 25100, Pakistan*
[n] *Pharmacy Discipline, School of Life Sciences, Khulna University, Khulna, 9208, Bangladesh*
[o] *Gaco Pharmaceuticals and Research Laboratory, Dhaka, 1000, Bangladesh*
[p] *College of Medicine and Public Health, Flinders University, Bedford Park, 5042, Australia*
[q] *Cancer Biology Laboratory, School of Biological Sciences (Zoology), Dr. Harisingh Gour Central University, Sagar, 470003, M.P, India*
[r] *Department for Management of Science and Technology Development, Ton Duc Thang University, Ho Chi Minh City, Viet Nam*
[s] *Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City, Viet Nam*
[t] *Department of Chemistry, The University of Jordan, Amman, 11942, Jordan*

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Animal model

ABSTRACT

Epilepsy is a neurological disease affecting people of all ages worldwide. Side effects of antiepileptic drugs and their association with oxidative stress stimulate the search for new drugs, which would be more affordable with fewer adverse effects. Accordingly, the aim of the present work is to evaluate the anticonvulsant effect of anacardic acid (AA), a natural compound extracted from cashew liquid (*Anacardium occidentalis*), in murine models, as well as its antioxidant actions in *Saccharomyces cerevisiae*. AA (> 90% purity) was tested, *in vivo*, in male Swiss mice (25–30 g) with four convulsive models, (1) pentylenetetrazole, (2) pilocarpine, (3) electroshock, and (4) kainic acid, at doses of 25, 50, and 100 mg/kg, body weight (B.W.) Additionally, the effective dose, toxic dose, and protective index studies were also performed. Results revealed that AA exhibits anticonvulsive effects in models 1, 3, and 4, with a mean effective dose (ED_{50}) of 39.64 (model 1) > 100 mg/kg, B.W. (model 2), and

Abbreviations: AA, anacardic acid; AED, antiepilectic drugs; KA, kainic acid; PIL, pilocarpine; PTZ, pentylenetetrazole; ROS, reactive oxygen species; RNS, reactive nitrogen species; CNS, central nervous system; SOD, superoxide dismutase; $GABA_A$, gamma(γ)-aminobutyric acid; LCC, liquid of cashew nuts; LIFS, latency installation of first seizure; FLU, flumazenil; DMSO, dimethylsulfoxide; GC–MS, gas chromatography–mass spectrometry; MES, electroshock model; BDZ, benzodiazepines; DZP, diazepam; QUE, quercetin; DPPH, 1,1-diphenyl-2-picrylhydrazyl

* Corresponding author at: Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City, Viet Nam.
** Corresponding author at: Department of Chemistry, The University of Jordan, Amman 1149, Jordan.
E-mail addresses: muhammad.torequl.islam@tdt.edu.vn (M.T. Islam), mmubarak@ju.edu.jo (M.S. Mubarak).
[1] Present address: Department of Biochemistry and Molecular Genetics, Northwestern University Feinberg School of Medicine, 320 E Superior St, Chicago, IL 60611, USA.

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Pharmacology

AGOMELATINE TREATMENT CORRECTS DEPRESSIVE-LIKE BEHAVIOUR INDUCED BY CHRONIC CONSTANT LIGHT EXPOSURE THROUGH MODULATION OF CIRCADIAN RHYTHM OF CORTICOSTERONE RELEASE

Jana Tchekalarova, Tsveta Stoyanova, Rumyana Gesheva, Milena Atanasova*

(*Submitted by Academician P. Vassileva on September 18, 2017*)

Abstract

Exposure to chronic constant light (CCL) affects diurnal rhythms and provokes depression in experimental animals. The aim of the present study was to explore the effect of continuous treatment with the clinically used antidepressant agomelatine, a potent melatonin MT_1 and MT_2 receptor agonist and serotonin $5HT_{2C}$ receptor antagonist, on depressive symptoms induced by CCL and diurnal rhythm of plasma corticosterone concentration. Male Wistar rats exposed to CCL for three weeks showed anhedonia in sucrose preference test (SCT), increased immobility in forced swimming test (FST) during the dark phase of day/light regimen and loss of diurnal patterns of corticosterone in plasma. Chronic agomelatine treatment, at a dose of 40 mg/kg for three weeks, prevented depressive behaviour and restored disrupted rhythm of corticosterone release. Taken together, a depressive-like behaviour is associated by a disrupted rhythm of plasma corticosterone level in CCL model in rats. Agomelatine is able to prevent depressive responses through correction of diurnal rhythm of corticosterone in plasma.

Key words chronic constant light, depression, corticosterone, agomelatine, Wistar rat

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Antidepressant agomelatine attenuates behavioral deficits and concomitant pathology observed in streptozotocin-induced model of Alzheimer's disease in male rats

Kalina Ilieva[b], Jana Tchekalarova[b], Dimitrinka Atanasova[b,c,d], Lidia Kortenska[a], Milena Atanasova[a,*]

[a] Department of Biology, Medical University of Pleven, 1 Kliment Ohridski Str., Pleven 5800, Bulgaria
[b] Institute of Neurobiology, Acad. G. Bonchev Str., Bl. 23, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria
[c] Department of Anatomy, Faculty of Medicine, Trakia University, 11 Armeiska Str, Stara Zagora 6003, Bulgaria
[d] Department of Genes and Behavior, Max Planck Institute of Biophysical Chemistry, Gottingen 37077, Germany

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ABSTRACT

Experimental findings suggest that the melatonin system has a beneficial role in models of Alzheimer's disease (ADs). The aim of the present study was to explore whether the atypical antidepressant agomelatine (Ago), which is a melatonin MT_1 and MT_2 agonist and $5\text{-}HT_{2C}$ antagonist, is effective against behavioral, biochemical and histological impairments in streptozotocin (STZ)-induced model of ADs in male rats. Male Sprague Dawley rats were treated intraperitoneally (i.p.) with Ago (40 mg/kg) for 30 days starting three months following the intracerebroventricular (icv) injection of STZ. Chronic Ago treatment reduced anxiety-like behavior of STZ-treated rats in the elevated plus maze, increased the preference to saccharine and corrected the spatial memory impairment in the eight-arm radial arm maze test. This melatonin analogue restored STZ-induced biochemical changes, including an increase of beta amyloid (Aβ) protein, and signal markers of inflammation (TNF-alpha and IL-1 beta). Ago exerted partial neuroprotection, specifically in the temporal CA3b subfield of the dorsal hippocampus and temporal piriform cortex. The ability of Ago to alleviate behavioral symptoms and concomitant neuropathological events observed in a model of sporadic ADs suggests that this melatonin alternative can be considered a promising adjuvant in this disease.

1. Introduction

Depression is considered a risk factor for Alzheimer's disease (AD) (Ownby et al., 2006). Furthermore, depression is a frequent psychiatric disorder accompanying AD leading to higher rate of mortality in the elderly. Accumulated evidence suggest common underlying mechanism in patients with depression and comorbid depression in AD, including close genetic pathways in older adults (Modrego, 2010), a hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, a lack of feedback regulatory mechanism (Raadsheer et al., 1995), glutamatergic dysfunction, inflammation, cerebrovascular disease and altered synaptic plasticity (Chi et al., 2014; Dobos et al., 2012; Nihonmatsu-Kikuchi et al., 2013). Although an epidemiological link between the two diseases has been confirmed, there are few verified experimental models to support a shared pathology in both phenomena. Transgenic mouse models demonstrated that monoaminergic deficits associated with depression is a crucial condition for the development of AD (Liu et al., 2008; Romano et al., 2015). There are few recently published manuscripts describing that intracerebroventricular (icv) streptozotocin (STZ) model, which model represents 95% of sporadic AD, can provoke depressive-like behavior in animals. Thus, icv STZ-treated mice demonstrate increased immobility in tail suspension test and anhedonia (Souza et al., 2013, 2017), while rats exhibit decreased anxiety index in the elevated plus maze (EPM) test and depressive-like behavior in the forced swimming test (FST) (Navabi et al., 2018).

While commonly used antidepressants as selective serotonin re-uptake inhibitors (SSRIs) do not produce promising results as a therapeutic strategy for treatment of comorbid depression and AD, targets of inflammatory signaling (Siarkos et al., 2015), mood symptoms and cognitive impairment (Kiosses et al., 2015) or newly developed antidepressants with complex mechanism associated with effects on pre and post-synaptic monoaminergic pathway (Dale et al., 2015) can provide

* Corresponding author at: Medical University - Pleven, 1 Kliment Ohridski Str., Pleven 5800, Bulgaria.
E-mail address: milenaar2001@yahoo.com (M. Atanasova).

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ORIGINAL INVESTIGATION

Agomelatine treatment corrects impaired sleep-wake cycle and sleep architecture and increases MT_1 receptor as well as BDNF expression in the hippocampus during the subjective light phase of rats exposed to chronic constant light

Jana Tchekalarova[1] · Lidia Kortenska[1] · Natasha Ivanova[1] · Milena Atanasova[2] · Pencho Marinov[3]

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Abstract

Rationale Exposure to chronic constant light (CCL) has a detrimental impact on circadian rhythms of motor activity and sleep/wake cycles. Agomelatine is an atypical antidepressant showing a chronotropic activity.

Objectives In this study, we explored the role of melatonin (MT) receptors and brain-derived neurotrophic factor (BDNF) in the brain in the mechanism underlying the effects of agomelatine on diurnal variations of motor activity, sleep/wake cycle, and sleep architecture in a rat model of CCL.

Methods In *Experiment #1*, home cage activity was monitored automatically with cameras for a period of 24 h. The diurnal rhythm of MT_1, MT_2 receptors, and BDNF expression in the hippocampus and frontal cortex (FC), was tested using the ELISA test. In *Experiment #2*, rats were equipped with electroencephalographic (EEG) and electromyographic (EMG) electrodes and recordings were made under basal conditions (12:12 LD cycle + vehicle), LL + vehicle and LL + agomelatine (40 mg/kg/day for 21 days).

Results The rats exposed to CCL showed an impaired diurnal rhythm of motor activity and sleep/wake cycle with reduced NREM sleep and *delta* power and increased REM sleep and *theta* power. The duration and number of episodes of the wake were diminished during the subjective dark phase in this group. The circadian rhythm of MT_1 and MT_2 receptors and their expression did not change in the hippocampus and FC under CCL exposure, while the BDNF levels in the hippocampus decreased during the subjective light phase. Agomelatine restored the diurnal rhythm of motor activity, disturbed sleep/wake cycle, and sleep architecture, which effect was accompanied by an increase in MT_1 receptor and BDNF expression in the hippocampus at 10:00 in CCL rats.

Conclusions These findings support the value of agomelatine as an antidepressant that can adjust circadian homeostasis of motor activity and sleep/wake cycle in a CCL model.

Keywords Chronic constant light · Agomelatine · Motor activity · Sleep/wake cycle · MT receptors · BDNF

Introduction

The sleep/wake cycle, considered a core pattern of the mammalian circadian system, has complex regulation, which involves different brain pathways and structures (Saper et al. 2005). Chronic disturbance in sleep/wake patterns occurs in the majority of individuals who have experienced depression. Patients suffering from depression are reported to have a shorter latency and exacerbated REM sleep, accompanied by a loss of *delta* wave-related sleep compared to healthy subjects (Shaffery et al. 2003; Tsuno et al. 2005). Impaired circadian rhythm of melatonin secretion has also been reported in depression (Koenigsberg et al. 2004; Rabe-Jabłońska and

✉ Jana Tchekalarova
janetchekalarova@gmail.com; jane@bio.bas.bg

[1] Institute of Neurobiology, Bulgarian Academy of Sciences (BAS), 1113 Sofia, Bulgaria

[2] Department of Biology, Medical University of Pleven, 5800 Pleven, Bulgaria

[3] Institute of Information and Communication Technologies, BAS, 1113 Sofia, Bulgaria

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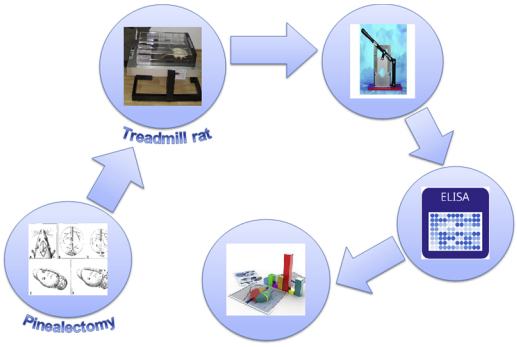
Research article

Effect of endurance training on diurnal rhythms of superoxide dismutase activity, glutathione and lipid peroxidation in plasma of pinealectomized rats

Jana Tchekalarova[a,*], Tzveta Stoyanova[a], Zlatina Nenchovska[a], Natasha Ivanova[a], Dimitrinka Atanasova[a,b], Milena Atanasova[c], Katerina Georgieva[d]

[a] Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia, 1113, Bulgaria
[b] Department of Biology, Medical University of Pleven, 1 Kliment Ohridski Str., Pleven, 5800, Bulgaria
[c] Department of Anatomy, Faculty of Medicine, Trakia University, Stara Zagora, Bulgaria
[d] Department of Physiology, Medical University-Plovdiv, Bulgaria

GRAPHICAL ABSTRACT



ARTICLE INFO

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Melatonin deficit
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MDA

ABSTRACT

Melatonin deficit is characterized by disturbed circadian rhythms of many physiological and biochemical parameters including markers of oxidative stress. Moderate endurance training exerts protection against oxidative stress. In the present study, we aimed to explore the impact of endurance treadmill training on disturbed rhythmic fluctuations of some markers of oxidative stress in pinealectomized rats. Animals were divided into four groups: sham-operated sedentary rats (sham-sed), a sham group with exercise (sham-ex), pinealectomized sedentary rats (pin-sed) and pin rats with exercise (pin-ex). Animals were sacrificed by decapitation at 4-h intervals for biochemical analysis of plasma melatonin and markers of oxidative stress. The activity of superoxide dismutase (SOD) and the levels of glutathione (GSH) and lipid peroxidation demonstrated diurnal variations in the sham-sed group. The peak values of SOD were detected during the dark period that coincided with the peak plasma levels of melatonin in the sham-sed rats. The malondialdehyde (MDA) levels also showed a tendency to a progressive raise during the dark period. Pinealectomy was characterized by a remarkable melatonin deficit in plasma of sedentary rats, compromised fluctuations with decreased SOD activity and increased lipid peroxidation. While endurance training was unable to restore the melatonin deficit, it partly prevented the

* Corresponding author at: Institute of Neurobiology, Acad. G. Bonchev Str., Bl. 23, Bulgarian Academy of Sciences, Sofia, 1113, Bulgaria.
E-mail address: janetchekalarova@gmail.com (T. Jana).

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Endurance training exerts time-dependent modulation on depressive responses and circadian rhythms of corticosterone and BDNF in the rats with pinealectomy

Jana Tchekalarova[a,*], Milena Atanasova[b], Natasha Ivanova[a], Nickolay Boyadjiev[c], Rumyana Mitreva[a], Katerina Georgieva[c]

[a] Institute of Neurobiology, Bulgarian Academy of Sciences (BAS), Sofia, 1113, Bulgaria
[b] Department of Biology, Medical University of Pleven, Pleven, 5800, Bulgaria
[c] Department of Physiology, Medical University-Plovdiv, Bulgaria

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ABSTRACT

Pinealectomy can cause a disturbance in emotional status and circadian rhythms of the endocrine and metabolic functions in the body. Endurance training is considered a part of the complex therapy of dysfunctions driven by changes in circadian dynamics of many physiological indicators. In the present study, we aimed to study the effect of endurance training on depressive behavior induced by pinealectomy in rat. We tested the hypothesis that endurance training can have a beneficial impact on depressive behavior induced by pinealectomy in rat via correction of desynchronized circadian rhythms of corticosterone secretion in plasma and brain-derived neurotrophic factor (BDNF) in the hippocampus. The continuous exercise program attenuated depressive responses characterized by the disrupted diurnal rhythm of home-cage motor activity, anhedonia in the sucrose preference test, decreased grooming in the splash test, and despair-like behavior in the forced swimming test of rats with pinealectomy to values resembling those of sham-treated controls. Parallel to the observed positive effect on the emotional status, exercise training diminished total plasma corticosterone levels and corrected its flattened pattern. While the melatonin deficiency did not affect the fluctuations of the BDNF levels, the exercise program induced a considerable and time-dependent increase in its level. These findings suggest that the antidepressant-like effect of endurance training might be mediated via correction of the disturbed circadian rhythm of corticosterone release and enhancement of hippocampal BDNF levels in rats with pinealectomy. Therefore, this alternative mode might have a potential therapeutic application in a subpopulation of people characterized by a melatonin deficiency.

1. Introduction

The hight dynamic and stressful style of life nowadays is a factor predisposing to increased risk of developing a neuropsychiatric disorder, including depression that affects both mood and psychical state. The impaired sleep-wake cycle is considered a crucial factor associated with the pathophysiology of mood disorders. Modern technology gives opportunities for adjusting activities independently of the main external synchronizer, the light. In this line, different habits related to contemporary life can affect the normal biological rhythms of the body, including the increased time of night activity, including work at night, shift work, long-distance flights across several time zones (jet-lag syndrome) and thereby predispose to mood disorders (Salgado-Delgado et al., 2011; Waterhouse et al., 2007). Accumulated data from patients with depression and experimental models suggest that the link between the development of depression and disturbance in circadian rhythms of wake activity, sleep architecture, core temperature, hormonal release and metabolism is positive and reciprocal (Kronfeld-Schor and Einat, 2012; Salgado-Delgado et al., 2011; Souêtre et al., 1989). Patients with depression have a disturbed rhythm of activity, measured by actigraphy, e.g., diminished motor activity during the day while increased at night (Kronfeld-Schor and Einat, 2012; Volkers et al., 2003).

The primary hormone released by the pineal gland at dark, melatonin is an essential endogenous hormone with chronobiotic activity involved in the regulation of circadian rhythms of different physiological processes and their synchronization with external stimuli like the

* Correspondent author.
E-mail addresses: bio.bas@bg.com, janetchekalarova@gmail.com (J. Tchekalarova).

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Plasma lipoprotein(a) concentration as an independent predictor of hemodynamic progression of aortic valve stenosis

Vesela D. Tomova[1] · Margarita L. Alexandrova[2] · Milena A. Atanasova[3] · Maria L. Tzekova[4] · Tihomir R. Rashev[5] · Sarfraz Ahmad[6]

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Abstract

Calcific aortic valve disease (CAVD) is a common cardiovascular disorder of high social significance. This study aimed to identify independent predictors of hemodynamic progression of CAVD. The relationship between some risk factors, including the rs10455872 polymorphism in the intron 25 of the lipoprotein(a) [Lp(a)] coding region and the plasma Lp(a) concentration, and CAVD severity were prospectively examined in 114 patients. Age ($p=0.023$), smoking ($p=0.038$), lack of obesity ($p=0.005$), triglyceride levels ($p=0.039$), and plasma Lp(a) ($p<0.0001$) levels were found to be significant determinants of stenosis progression. The rs10455872 polymorphism; however, was not found to be a significant factor for neither the stenosis severity ($p=0.773$) nor for plasma Lp(a) levels ($p=0.617$). We established a highly significant Lp(a) cut-off concentration (21.2 mg/dL) distinguishing the aortic valve calcification without stenosis from the significant stenosis. Plasma Lp(a) concentration was the only independent predictor of disease progression ($p<0.0001$). Moreover, patients with plasma levels of Lp(a) $\geq$ 21.2 mg/dL were 55 times more likely to develop aortic valve stenosis. We conclude that Lp(a) concentration may prove valuable for more reliable identification of patients at risk of accelerated CAVD development. Future studies are desirable to determine whether plasma Lp(a) levels could be used as a potential biomarker for aortic stenosis progression.

Keywords Calcific aortic valve disease · Lipoprotein (a) · rs10455872 polymorphism · Aortic stenosis progression · Independent predictors · Binary logistic regression

Introduction

Calcific aortic valve disease (CAVD) ranks third among the most prevalent cardiovascular disorders in adult and advanced age (after arterial hypertension and ischemic heart disease). It is the second most common cause of cardiac surgery interventions in the countries of Europe and the North America after aortic-coronary bypass. This disease is of high social significance not only because it is widespread, but also because it can progress sub-clinically for a long time (for an average of 7–8 years). With severe aortic stenosis, the 2-year survival rate without surgical interventions is at about 50% [1].

In the recent decades, some studies have been performed on the etiopathogenesis of the disease and the risk factors influencing its onset and development. Various predictors of aortic valve calcification have been identified, including age, diabetes mellitus, metabolic syndrome, pulse rate, arterial hypertension, body mass index (BMI), smoking, disturbances of renal function, and calcium-phosphate metabolism

✉ Vesela D. Tomova
vessela.dimova@gmail.com

✉ Sarfraz Ahmad
sarfraz.ahmad@AdventHealth.com

[1] Department of Internal Diseases, University Hospital "St. Marina" - Pleven, Medical University – Pleven, 5800 Pleven, Bulgaria

[2] Department of Biophysics, Medical University – Pleven, Pleven, Bulgaria

[3] Department of Biology, Medical University – Pleven, Pleven, Bulgaria

[4] Second Clinic of Cardiology, University Hospital, "Dr. G. Stranski" – Pleven, Medical University – Pleven, Pleven, Bulgaria

[5] Department of Anatomy, Histology, Cytology and Biology, Medical University – Pleven, Pleven, Bulgaria

[6] AdventHealth Medical Center, 2501 N. Orange Ave., Suite 786, Orlando, FL 32804, USA

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ORIGINAL PAPER

RELATIONSHIPS BETWEEN HEPCIDIN, INTERLEUKIN-6 AND PARAMETERS OF IRON METABOLISM IN PREGNANT WOMEN

Tsvetelina V. PETKOVA-MARINOVA[1]✉, Boryana K. RUSEVA[1], Bozhanka PANEVA-BARZASHKA[2], Milena A. ATANASOVA[3], Petya V. DRAGOMIROVA[3], Pavlina D. LALEVA[4]

[1] Department of Physiology, Faculty of Medicine, Medical University – Pleven, Bulgaria
[2] Medical Center for Reproductive Medicine – Pleven, Bulgaria
[3] Department of Biology, Faculty of Medicine, Medical University – Pleven, Bulgaria.
[4] Department of Pre-clinical and Clinical Sciences, Faculty of Pharmacy, Medical University – Pleven, Bulgaria

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Abstract

Introduction. Iron homeostasis has been extensively studied in the recent years. The factors regulating hepcidin secretion and the significance of hepcidin during pregnancy have not been fully clarified.
The objective of the study was to investigate the serum concentrations of hepcidin and interleukin-6 (IL-6) and their relationships to parameters of iron metabolism in women with low-risk and high-risk pregnancies.
Material and methods. The study involved 40 pregnant women distributed in two groups: high-risk pregnancies (HRP, n=20) and low-risk pregnancies (LRP, n=20). The HRP were associated with chronic inflammatory disorders and reproductive failures. We evaluated the red blood cell count, hemoglobin (Hb) concentration, hematocrit (Hct), erythrocyte indices, serum concentrations of hepcidin, IL-6, ferritin (Ferr) and iron (Fe), the total iron binding capacity (TIBC)

Résumé

Relations entre l'hepcidine, l'interleukine-6 et les paramètres du métabolisme du fer chez les femmes enceintes

Introduction. La régulation de l'homéostasie du fer a été largement étudiée ces dernières années. Les facteurs régulateurs de la sécrétion d'hepcidine et la signification de l'hepcidine pendant la grossesse n'ont pas été entièrement clarifiées.
L'objectif de l'étude était d'explorer les concentrations sériques d'hepcidine et d'interleukine-6 (IL-6) et leurs relations avec les paramètres du métabolisme du fer chez les femmes aux grossesses à faible et à haut risque.
Matériel et méthodes. L'étude a porté sur 40 femmes enceintes réparties en deux groupes: les grossesses à haut risque (GHR, n = 20) et les grossesses à faible risque (GFR, n=20). Les GHR étaient associées

✉ Address for correspondence: Tsvetelina V. PETKOVA-MARINOVA
Department of Physiology, Faculty of Medicine, Medical University – Pleven, Bulgaria
Address: 1, St. Kliment Ohridski Str., 5800 Pleven, Bulgaria
E-mail: cveti_doc@abv.bg; Phone: + 359 64 884 182

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ORIGINAL RESEARCH

Chronic Piromelatine Treatment Alleviates Anxiety, Depressive Responses and Abnormal Hypothalamic–Pituitary–Adrenal Axis Activity in Prenatally Stressed Male and Female Rats

Natasha Ivanova[1] · Zlatina Nenchovska[1] · Milena Atanasova[2] · Moshe Laudon[3] · Rumyana Mitreva[1] · Jana Tchekalarova[1]

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Abstract

The prenatal stress (PNS) model in rodents can induce different abnormal responses that replicate the pathophysiology of depression. We applied this model to evaluate the efficacy of piromelatine (Pir), a novel melatonin analog developed for the treatment of insomnia, in male and female offspring. Adult PNS rats from both sexes showed comparable disturbance associated with high levels of anxiety and depressive responses. Both males and females with PNS demonstrated impaired feedback inhibition of the hypothalamic–pituitary–adrenal (HPA) axis compared to the intact offspring and increased glucocorticoid receptors in the hippocampus. However, opposite to female offspring, the male PNS rats showed an increased expression of mineralocorticoid receptors in the hippocampus. Piromelatine (20 mg/kg, i.p., for 21 days injected from postnatal day 60) attenuated the high anxiety level tested in the open field, elevated plus-maze and light–dark test, and depressive-like behavior in the sucrose preference and the forced swimming tests in a sex-specific manner. The drug reversed to control level stress-induced increase of plasma corticosterone 120 min later in both sexes. Piromelatine also corrected to control level the PNS-induced alterations of corticosteroid receptors only in male offspring. Our findings suggest that the piromelatine treatment exerts beneficial effects on impaired behavioral responses and dysregulated HPA axis in both sexes, while it corrects the PNS-induced changes in the hippocampal corticosteroid receptors only in male offspring.

Keywords Prenatal stress · Piromelatine · Sex differences · Behavior · HPA axis · Corticosteroid receptors

Introduction

The prenatal period represents a critical time for brain development. Exposure to stressful events during pregnancy can provoke a net of devastating processes with a high impact on epigenetic factors. The latter can lead to re-programming in brain maturation resulting in long-term consequences in the offspring. Major depressive disorder represents a delayed outcome resulting from the suppressive effects of stress on prenatal development (Darnaudéry and Maccari 2008; Heim et al. 2009; Lupien et al. 2009; Weinstock 2008). The model of prenatal stress (PNS) is associated with many neurobiological disturbances resembling the pathophysiology of patients with depression. Offsprings of PNS rats have been characterized by abnormal circadian rhythmicity of important parameters linked with dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis (Maccari et al. 1995), a condition considered a relevant model of depression (Mairesse et al. 2015). In this line, experimental studies have revealed that in rodents PNS causes long-term harmful effects on brain functions associated with behavioral changes (Głombik et al. 2015; Schmidt et al. 2018; Vallée et al. 1997; Weinstock 2001), desynchronized circadian rhythms of the sleep–wake cycle, motor activity and corticosterone (CORT) secretion (Koehl et al. 1999; Morley-Fletcher et al. 2019). Being age-dependent, neurobiological disturbances

✉ Natasha Ivanova
ivanova_nm@yahoo.com

✉ Jana Tchekalarova
janetchekalarova@gmail.com

[1] Institute of Neurobiology, Bulgarian Academy of Sciences, Acad. G. Bonchev St., Bl. 23, 1113 Sofia, Bulgaria

[2] Department of Biology, Medical University of Pleven, 5800 Pleven, Bulgaria

[3] Drug Discovery, Neurim Pharmaceuticals Ltd., Tel-Aviv, Israel

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Chronic agomelatine treatment alleviates icvAβ-induced anxiety and depressive-like behavior through affecting Aβ metabolism in the hippocampus in a rat model of Alzheimer's disease

Kalina Ilieva [a], Milena Atanasova [a,*], Dimitrinka Atanasova [b,c], Lidia Kortenska [b], Jana Tchekalarova [b,1]

[a] Department of Biology, Medical University of Pleven, 1 Kliment Ohridski Str., Pleven 5800, Bulgaria
[b] Institute of Neurobiology, Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Bl. 23, Sofia 1113, Bulgaria
[c] Department of Anatomy, Faculty of Medicine, Trakia University, 11 Armeiska Str, Stara Zagora 6000, Bulgaria

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ABSTRACT

Recently, we reported that the atypical antidepressant agomelatine (Ago) exerted a beneficial impact on behavioral changes and concomitant neuropathological events in icvSTZ rat model of sporadic Alzheimer diseases (AD). In the present study, we aimed to explore the effect of Ago (40 mg/kg, i.p. for 30 days) on beta-amyloid (Aβ) metabolism in icv$Aβ_{1–42}$ rat model of AD. The melatonin analogue was administered either simultaneously with $Aβ_{1–42}$ (AβAgo1) or 30 days later during the late stage of the progression of AD (AβAgo2). Treatment with Ago in the early stage of AD attenuated anxiety and depressive-like responses but was inefficient against Aβ-induced impairment of hippocampus-dependent spatial memory. The melatonin analogue, administered both during the early and the late stage of AD, corrected to control level the elevated $Aβ_{1–42}$ in the frontal cortex (FC) and the hippocampus. The concentration of α-secretase was enhanced by AβAgo1 compared to the sham- and Aβ-veh groups in the hippocampus. No changes in the concentration of β-secretase in the FC and the hippocampus as well as of γ-secretase in the FC were observed among groups. Both the AβAgo1 and AβAgo2 attenuated to control level the Aβ-induced increased concentration of γ-secretase in the hippocampus. AβAgo1 exerted also structure-specific neuroprotection observed mainly in the CA1, septal CA3b subfield of the dorsal hippocampus and septo-temporal piriform cortex (Pir) and partially in the temporal CA3c, septal and temporal Pir. These findings suggest that Ago treatment in the early stage of AD can exert beneficial effects on concomitant behavioral impairments and neuroprotection in associated brain structures. The antidepressant administration both in the early stage and after the progression of AD affected Aβ metabolism via decreasing of γ-secretase concentration in the hippocampus.

1. Introduction

Considered one of the most devastating neurodegenerative diseases, Alzheimer's disease (AD) is expected to affect over 115 million people by 2050 [28]. The behavioral symptomatic of AD is mainly associated with a progressive decline in cognitive function and dementia [31]. While impaired memory capacity is considered an essential hallmark of AD, one-third of patients demonstrate psychiatric symptoms with emotional complications, sleep disturbance, anxiety, and depression [1, 24]. The pathology of AD is closely related to the accumulation of extracellular amyloid-β (Aβ) ($Aβ_{40}$ and $Aβ_{42}$ isoforms of Aβ). The formation of AD-associated senile plaques is mainly due to the $Aβ_{42}$ isoforms [10, 45] and later intracellular neurofibrillary tangles of hyperphosphorylated tau neurofibrillary tangles, which cause synaptic dysfunction and neuronal loss [44]. However, Aβ pathological metabolism is earlier and precedes the formation of tau tangles and the AD symptoms [4, 20]. Clinical data suggest that there is a bidirectional link between depression and AD, and probably the two disorders might share a common pathogenic pathway [5, 24]. The essential role of changes in Aβ metabolism is considered one of the possible underlying mechanisms

* Address for correspondence: Medical University - Pleven, 1 Kliment Ohridski Str., Pleven 5800, Bulgaria
E-mail addresses: milenaar2001@yahoo.com (M. Atanasova), janetchekalarova@gmail.com (J. Tchekalarova).
[1] Institute of Neurobiology, Acad. G. Bonchev Str., Bl. 23, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria

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Article

Estimation of *Ixodes ricinus* (Acari: Ixodidae) Populations of Kaylaka Park in the Town of Pleven, Bulgaria

Alexander Blazhev [1,*], Milena Atanasova [1], Krasimir Kostov [2], Tsetsa Doychinova [3], Svetla Blazheva [4] and Milena Karcheva [3]

[1] Department of Biology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; milena.atanasova-radeva@mu-pleven.bg
[2] Department of Pathophysiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; dr.krasi_kostov@abv.bg
[3] Department of Infectious Diseases and Epidemiology, Medical University-Pleven, 1 Kliment Ohridski Str., 5800 Pleven, Bulgaria; doichinova_ceca@abv.bg (T.D.); milena_karcheva@abv.bg (M.K.)
[4] Department of Immunology, University Hospital, 5800 Pleven, Bulgaria; svetlabl@abv.bg
* Correspondence: yalishanda9@gmail.com; Tel.: +35-(99)-88986865

Simple Summary: Hard ticks transmit the etiological agents of numerous diseases. Kaylaka Park is a protected area, but part of it is designated for various outdoor activities. The aim of our study was to establish the presence of hard ticks in four urbanized areas and four areas that are not maintained and are natural wilderness areas (wild areas). The flagging method of collection was used. Temperature, relative humidity, both collection time and distance covered were measured during the sampling campaigns. The density of ticks collected was calculated, the number of ticks captured per minute was calculated and the results were compared between urban and wild areas over a five-year period (2016–2020). A total of 622 ticks were collected. All of them were identified as *Ixodes ricinus*. Significant differences between the urban and wild areas were observed in the number of ticks per minute and density of nymphs. The peak in questing tick activity has been established at the end of April. The highest yield was obtained at 20 °C and at 60% relative humidity. We found that the distribution of *Ixodes ricinus* ticks is widespread in Kaylaka Park. Their high density poses a serious risk to park visitors in both wild and maintained urban areas.

Abstract: (1) Background: Ticks are vectors of a large number of pathogenic microorganisms, which cause serious diseases in both humans and animals. Kaylaka Park is located in northern Bulgaria close to the city of Pleven. Part of the park is urbanized and visited daily by many citizens. The aim of our study was to determine the presence and distribution of hard ticks in the park area by surveying and comparing four urbanized with four wild areas. (2) Methods: Ticks were collected by flagging from 2016 to 2020 during the spring–summer season (March–July). Air temperature, relative humidity, collection time and flagging area were measured during the campaign. (3) Results: A total of 622 ticks were collected: 285 females (46%), 272 (44%) males and 64 (10%) nymphs. All were identified as *Ixodes ricinus*. Wild areas showed statistically significant higher values of ticks collected per minute ($p = 0.009$) and nymph densities ($p = 0.003$) compared to urbanized sampling sites. Other densities indices did not have a significant difference between urban and wild areas. Highest numbers of *Ixodes* ticks were collected at a temperature of 20 °C and at 60% relative humidity. The active questing began in March, peaked in end of April and declined in June. (4) Conclusions: In the present study, we found that ecological factors in the Kaylaka Park area are favourable for the development and distribution of tick populations. The results give us reason to consider that there is a high risk to visitors from tick bites in the Kaylaka Park area.

Keywords: *Ixodes ricinus*; tick collection; tick density; flagging; medical entomology; Kaylaka Park

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Article

Anticonvulsant Effects of Topiramate and Lacosamide on Pilocarpine-Induced Status Epilepticus in Rats: A Role of Reactive Oxygen Species and Inflammation

Michaela Shishmanova-Doseva [1,*], Lyudmil Peychev [1], Lyubka Yoanidu [2], Yordanka Uzunova [2], Milena Atanasova [3], Katerina Georgieva [4] and Jana Tchekalarova [5,*]

[1] Department of Pharmacology and Drug Toxicology, Medical University-Plovdiv, 4002 Plovdiv, Bulgaria; peych@propolisbg.com
[2] Department of Bioorganic Chemistry, Medical University-Plovdiv, 4002 Plovdiv, Bulgaria; lubka.yoanidu@gmail.com (L.Y.); d_anny@abv.bg (Y.U.)
[3] Department of Biology, Medical University of Pleven, 5800 Pleven, Bulgaria; milenaar2001@yahoo.com
[4] Department of Physiology, Medical University-Plovdiv, 4002 Plovdiv, Bulgaria; kng@plov.net
[5] Institute of Neurobiology, Bulgarian Academy of Sciences (BAS), 1113 Sofia, Bulgaria
* Correspondence: shishmanovamichaella@gmail.com (M.S.-D.); janetchekalarova@gmail.com (J.T.); Tel.: +359-888-653-476 (M.S.-D.); +359-887-267-052 (J.T.)

Abstract: Background: Status epilepticus (SE) is a neurological disorder characterized by a prolonged epileptic activity followed by subsequent epileptogenic processes. The aim of the present study was to evaluate the early effects of topiramate (TPM) and lacosamide (LCM) treatment on oxidative stress and inflammatory damage in a model of pilocarpine-induced SE. Methods: Male Wistar rats were randomly divided into six groups and the two antiepileptic drugs (AEDs), TPM (40 and 80 mg/kg, i.p.) and LCM (10 and 30 mg/kg, i.p.), were injected three times repeatedly after pilocarpine administration. Rats were sacrificed 24 h post-SE and several parameters of oxidative stress and inflammatory response have been explored in the hippocampus. Results: The two drugs TPM and LCM, in both doses used, succeeded in attenuating the number of motor seizures compared to the SE-veh group 30 min after administration. Pilocarpine-induced SE decreased the superoxide dismutase (SOD) activity and reduced glutathione (GSH) levels while increasing the catalase (CAT) activity, malondialdehyde (MDA), and IL-1β levels compared to the control group. Groups with SE did not affect the TNF-α levels. The treatment with a higher dose of 30 mg/kg LCM restored to control level the SOD activity in the SE group. The two AEDs, in both doses applied, also normalized the CAT activity and MDA levels to control values. In conclusion, we suggest that the antioxidant effect of TPM and LCM might contribute to their anticonvulsant effect against pilocarpine-induced SE, whereas their weak anti-inflammatory effect in the hippocampus is a consequence of reduced SE severity.

Keywords: status epilepticus; anticonvulsants; oxidative stress; IL-1β; TNF-α; hippocampus

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1. Introduction

Status epilepticus (SE) is a clinical condition characterized by prolonged or short-term but repeated seizures activity [1]. It results in epileptogenesis with devastating plastic changes in vulnerable brain structures, including decreased seizure threshold and neuronal injury [2,3]. SE may develop in already diagnosed epilepsy patients, due to the pathological hypersynchronized activity and the excitability of the neurons [4]. Brain trauma, infections, ischemia/hypoxia, cerebrovascular diseases, and febrile conditions have been pointed out amongst the leading causes for the de novo development of this condition [5]. A variety of mechanisms including enhanced neuroinflammatory response and overproduction of reactive oxygen and nitrogen species are involved in the pathophysiology of SE and subsequent epileptogenic processes [6].

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Original article

ADAPTED MEDITERRANEAN DIET IMPACT ON THE SYMPTOMS OF CHRONIC FATIGUE, SERUM LEVELS OF OMEGA-3 POLYUNSATURATED FATTY ACIDS (PUFAS) AND INTERLEUKIN 17 (IL-17) IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS UNDERGOING DISEASE-MODIFYING THERAPY: A PILOT STUDY

Emiliya Ovcharova[1], Maya Danovska[1], Diana Marinova[1], Diana Pendicheva-Duhlenska[2], Pencho Tonchev[3], Milena Atanasova[4], Adelaida Ruseva[5], Nicholas Shepherd[6], Reni Tzveova[7]

1) Department of Neurology, Faculty of Medicine, Medical University – Pleven, Bulgaria.
2) Department of Pharmacology, Faculty of Pharmacy, Medical University – Pleven, Bulgaria.
3) Department of Surgical Nursing, Faculty of Health Care, Medical University – Pleven, Bulgaria.
4) Department of Biology, Faculty of Medicine, Medical University – Pleven, Bulgaria.
5) Department of Clinical Laboratory, Faculty of Medicine, Medical University – Pleven, Bulgaria
6) Department of Acute Medicine, Northampton General Hospital, UK.
7) Department of General and Clinical Pathology, University Hospital "Tsaritsa Yoanna" Sofia, Bulgaria.

SUMMARY

Purpose: This pilot study was designed to investigate the impact of a moderate-calorie Mediterranean diet compared to a regular diet with omega-3 PUFAs (eicosapentaenoic and docosahexaenoic acids) supplementation on fatigue symptoms in patients with relapsing-remitting multiple sclerosis (RRMS) and to assess the optional benefit of the diet on their quality of life.

Material/Methods: This 12-month pilot study was conducted in 2021 at the Department of Neurology, Medical University – Pleven, Bulgaria. A total of 60 patients with RRMS aged 18-64 were selected from the database of the Neurology Clinic at the University Hospital "Dr Georgi Stranski" – Pleven. From the selected patients, only 30 were included in the pilot phase and respectively assigned to the nutritional arms. Blood samples were collected twice – at the first and second visit in 3 months, for metabolic and dietary parameters analysis. Symptoms of fatigue were assessed with Fatigue Scale for Motor and Cognitive Functions (FSMC) and Modified Fatigue Impact Scale (MFIS).

Results: From the 30 participants included in the study, 17 patients attended the clinic centre for complete follow-up; the remaining 13 were only partially observed. The dynamics of the followed-up parameters showed a statistically significant change in the body mass index (BMI), the fatigue symptoms in the FSMC and MFIS scales, total cholesterol and triglycerides levels, and the serum concentrations of IL17A, EPA and DHA. The metabolic caloric values were also found to be significantly changed.

Conclusions: Despite the small study size limitation, this pilot study might be of benefit for further extensive research on the potential favorable impact of diet and lifestyle modifications on the symptoms of fatigue in multiple sclerosis patients.

Keywords: relapsing-remitting multiple sclerosis, Mediterranean diet, chronic fatigue, polyunsaturated fatty acids,

INTRODUCTION:

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating and neurodegenerative disease of the central nervous system (CNS) with female predominance and usual debut in the third or fourth decade of life. The molecular and tissue manifestation of systemic inflammation and varying degree of autoimmune process activation

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EMOTIONAL DISTURBANCE IN TWO MODELS OF MELATONIN DEFICIENCY: A COMPARATIVE STUDY

Zlatina Nenchovska, Milena Atanasova*, Natasha Ivanova, Rumyana Mitreva, Jana Tchekalarova#

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Abstract

In the present study, the aim was to compare the role of melatonin deficiency on emotional status in two different models, chronic constant light (CCL) and pinealectomy in male Wistar rats. While the rats with pinealectomy (Pin) showed impulsive behaviour (increased motor activity and lack of anxiety), CCL-rats demonstrated higher anxiety in the elevated plus-maze test (EPM). Slight differences in depressive-like behaviour, measured by the saccharine preference test (SPT) and the forced swimming test (FST), were also detected. The CCL-rats exhibited anhedonia only during the active (dark) phase of the light-dark cycle whereas rats with removed pineal gland showed depressive behaviour without diurnal variations. Immobility in the FST was increased in the two models of melatonin deficiency. Exposure to CCL and removal of the pineal gland abolished the circadian fluctuations in plasma melatonin levels. Both models of melatonin deficit exhibited higher plasma corticosterone levels during the light period and blunted diurnal variations of the hormone. Our findings suggest that models of melatonin deficiency recapitulate several neurobiological alterations associated with melancholic depression. Future studies are needed to elucidate the precise mechanism related to the model-specific difference in emotional status.

Key words: melatonin deficiency, emotional status, corticosterone, rat

#Corresponding author.

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The anticonvulsant effect of chronic treatment with topiramate after pilocarpine-induced status epilepticus is accompanied by a suppression of comorbid behavioral impairments and robust neuroprotection in limbic regions in rats

Michaela Shishmanova-Doseva [a,*], Dimitrinka Atanasova [b,c], Lyubka Ioanidu [d], Yordanka Uzunova [d], Milena Atanasova [e], Lyudmil Peychev [a], Jana Tchekalarova [b,*]

[a] Department of Pharmacology, Toxicology and Pharmacotherapy, Medical University of Plovdiv, Plovdiv 4002, Bulgaria
[b] Institute of Neurobiology, Bulgarian Academy of Sciences (BAS), Sofia 1113, Bulgaria
[c] Department of Anatomy, Faculty of Medicine, Trakia University, Stara Zagora 6003, Bulgaria
[d] Department of Bioorganic Chemistry, Medical University of Plovdiv, Plovdiv 4002, Bulgaria
[e] Department of Biology, Medical University of Pleven, Pleven 5800, Bulgaria

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ABSTRACT

Epilepsy is a widespread neurological disorder frequently associated with a lot of comorbidities. The present study aimed to evaluate the effects of the antiseizure medication topiramate (TPM) on spontaneous motor seizures, the pathogenesis of comorbid mood and cognitive impairments, hippocampal neuronal loss, and oxidative stress and inflammation in a rat model of temporal lobe epilepsy (TLE). Vehicle/TPM treatment (80 mg/kg, p.o.) was administered 3 h after the pilocarpine (pilo)-induced status epilepticus (SE) and continued for up to 12 weeks in Wistar rats. The chronic TPM treatment caused side effects in naïve rats, including memory disturbance, anxiety, and depressive-like responses. However, the anticonvulsant effect of this drug, administered during epileptogenesis, was accompanied by beneficial activity against comorbid behavioral impairments. The drug treatment suppressed the SE-induced neuronal damage in limbic structures, including the dorsal (CA1 and CA2 subfield), the ventral (CA1, CA2 and CA3) hippocampus, the basolateral amygdala, and the piriform cortex, while was ineffective against the surge in the oxidative stress and inflammation. Our results suggest that neuroprotection is an essential mechanism of TPM against spontaneous generalized seizures and concomitant emotional and cognitive impairments.

1. Introduction

Epilepsy is a widespread neurological disorder, with temporal lobe epilepsy (TLE) being one of the most common types of partial epilepsy, which are frequently associated with a lot of comorbidities, including cognitive impairment, mood, and behavioral problems [1,2]. Different animal models have been employed to study the mechanisms underlying the pathological changes occurring in TLE, where seizure activity is provoked by chemoconvulsant agents such as pilocarpine (pilo) or kainic acid [3,4]. Usually, spontaneous seizures have been generated during the first 4 to 6 weeks after the initial status epilepticus (SE), indicating that the normal brain has been transformed into an epileptic one, a process known as epileptogenesis [5]. Current literary data show that during SE, many functional and chemical changes occur in the brain, among which increased synthesis of free radicals as well as cytokines and chemokines, while during the chronic phase (weeks to months after SE) increased mossy fiber sprouting, gliosis, neuronal circuit reorganization, and hyperexcitability prevail [6]. All these changes have been pointed out as having major significance in the development of different comorbidities. Cognitive and psychiatric disorders disrupt the quality of life of affected individuals and thus should be addressed by clinicians [2]. One of the major pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), have been outlined as major contributors in the modulation of neuronal plasticity and long-term potentiation, which additionally aggravates cognitive impairment [7–9]. Immune cells are also known to produce as part of regular

* Corresponding authors.
E-mail addresses: shishmanovamichaella@gmail.com (M. Shishmanova-Doseva), bio.bas@bg.com (J. Tchekalarova).

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