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Antioxidant and Prooxidant Properties of a Polyphenol-rich Extract from *Geranium sanguineum* L. *In Vitro* and *In Vivo*

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A polyphenol-rich extract from *Geranium sanguineum* L. (PC) protected biological membranes due to its antioxidant capacity. PC caused a dose-dependent decrease of the osmotic hemolysis of human erythrocytes and increased their resistance against the toxic effect of H_2O_2; no effect on catalase activity was observed. While PC reduced the accumulation of TBA-reactive products in rat liver microsomes in inducible lipid peroxidation (LPO), the non-induced LPO was not affected.

Further the effect of PC on the products of LPO was investigated in the lungs, livers and sera of intact and influenza virus-infected mice (VIM). The infection enhanced LPO in the lungs and livers. In the group of PC-treated VIM, malondialdehyde (MDA) in the lungs and livers was brought to control levels. PC-treatment caused a significant increase of MDA in the lungs of intact mice, a slight one in the livers and did not affect MDA in the sera. Thus the extract exhibited prooxidant characteristics in intact animals as well as antioxidant properties in VIM. The reducing ability of PC on LPO could be an alternative mechanism of its protective effect in experimental influenza infection.

Keywords: plant polyphenols; biological membranes; lipid peroxidation; influenza virus infection.

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Structure-activity relationships of new L-Valine derivatives with neuropharmacological effects

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Four derivatives of L-Valine were studied as potential pharmacological agents. L-Valine is bound to either nicotinic (*m*-pyridinic) acid (M) or isonicotinic (*p*-pyridinic) acid (P) from N-side and to an alkyl fragment (or species) consisting of 3 or 6 methylene groups from C-side. In experiments *in vivo* (in albino mice) and *in vitro* (on cell cultures F4N) the compounds showed very low toxicity (intraperitoneal and oral toxicity over 2000 mg/kg and citotoxicity lower than vitamin C). At the same time, they demonstrated significant neuropharmacological activity. The experimental data obtained for their solubility in water and octanol, as well as with calculated log*P* correlate well with the results for their Central Nervous System effects.

Key words: L-Valine derivatives, neuropharmacological effect, pKa, logP, toxicity, *in vivo*, *in vitro*.

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Key words: L-Valine derivatives, neuropharmacological effect, pKa, logP, toxicity, *in vivo*, *in vitro*.

PROTECTIVE EFFECT OF POLYPHENOL-RICH EXTRACT ON ACUTE LUNG INJURY IN INFLUENZA VIRUS INFECTED MICE

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ABSTRACT

We have followed the anti-oxidant effects of a plant polyphenol-rich extract (PC) in the lungs of albino mice in the experimental influenza A/Aichi/2/68 (H3N2) (A/Aichi) virus infection. The effect of PC on the superoxide (O_2^-) and peroxide (H_2O_2) production from alveolar macrophages (aMØ) and on the lung antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) was studied. We also investigated the effect on the lipid peroxidation (LPO) and the total antioxidant activity (TAOA) in the lung tissue. All of the mentioned effects were studied in parallel with the protection on mortality rates and lung virological parameters on days 2, 6 and 9 after the viral challenge. It was shown that the extract significantly restored and stimulated the antioxidant activities in the lungs of influenza virus (IV)-infected mice. The protective effect of PC in the experimental influenza virus infection (EIVI) was related to both the specific antiviral effect of the extract and its antioxidant activity.

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New L- valine peptide mimetics as potential neuropharmacological agents

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Aim of the present study was to evaluate the effect of four recently synthesized peptide mimetics, derivatives of L-Valine, containing moieties of nicotinic/isonicotinic acids and hydrophobic spacers with two different lengths, on the cognitive functions of rodents. Male Albino mice were treated with these compounds in daily doses 125 and 250 mg/kg b. wt. for 3 consecutive days. Their learning and memory were evaluated with Step-through test, their exploratory activity with Hole-board test and their muscular coordination - with Rota-rod test. The ability of the used substances to affect metabolism of biogenic amines in hippocampus was studied in *Wistar* rats, 1 hour after single treatment (250 mg/kg i.p.). Our results revealed a significant dose-dependent effect of two of the compounds, which appear as positional isomers and contain longer hydrophobic spacer. Their effect on the parameters of learning and memory, exploratory activity and muscular coordination, was well pronounced. The levels of neuromediators in hippocampus were significantly changed after a single treatment. Serotonin (5-HT) levels were increased significantly by both compounds, one of which increased also noradrenaline levels. The improving effect on cognitive functions of rodents is most probably related to the presence of L-Valine, as well as nicotinic or isonicotinic residue. The much stronger influence of the pair with a longer hydrophobic spacer is due to the better lipid solubility and the possible blood-brain barrier transport related to it, so as to modulate biogenic neuromediators' levels in rat hippocampus.

Key words: peptide mimetics, L-valine, nicotinic acid derivatives, cognitive functions, neuromediators, neuropharmacological effect

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SEX-DEPENDENT EFFECT OF A NEW PEPTIDOMIMETIC ON COGNITIVE FUNCTION OF ISOLATED RATS AFTER MATERNAL DEPRIVATION

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ABSTRACT

INTRODUCTION: Maternal deprivation and social isolation lead to stress-related cognitive changes in rats. The aim of the study was to test the effect of the peptidomimetic M6 on postnatal stress in female and male rat offspring. MATERIAL AND METHODS: - Wistar pups were separated from their mothers on the 21st day, followed by 5-week isolation. Control rats were grouped in 2 cages: 6 male and 6 female. - Half the animals (grouped and isolated) received M6, 150 mg/kg/d (i.p.) for 3 days. - Exploratory activity, and learning and memory were tested with hole-board and step-through tests. - Data analysis was performed with SPSS, ANOVA (mixed design). RESULTS: The isolated rat pups were more exploratory active; in the same time they had better learning and memory than grouped animals. Cognitive functions were significantly better in male than in female isolated rats. Exploratory activity was less in male than in female grouped rats. The M6 effect on cognitive functions was sex-dependent: improved memory in male grouped animals and also in isolated female rats, but decreased memory in grouped female rats. CONCLUSION: Combined postnatal stress exposure (maternal deprivation, followed by social isolation) affects cognitive functions differently, depending specifically on gender and stress exposure.

Key words: maternal deprivation, social isolation, peptidomimetic, cognitive functions

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EFFECTS OF NEWLY-SYNTHESIZED PEPTIDE MIMETICS ON EXPLORATORY BEHAVIOUR, MEMORY AND SEROTONIN RELEASE IN THE HIPPOCAMPUS OF RATS WITH SOCIAL ISOLATION SYNDROME

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(*Submitted by Corresponding Member W. Ovtscharoff on July 6, 2012*)

Abstract

The effects of two newly-synthesized peptide mimetics (containing L-valine and nicotinamide/isonicotinamide residues) – M6 and P6 – were studied on Wistar rats after 6 weeks of social isolation. Their influence on changed cognitive functions in experimental aggression in rats was studied with the Hole board test (for exploratory behaviour) and also Step-through test on the 7th and on the 30th day (for short-term and long-term memory). The influence of the compounds on serotonin (5-HT) release in the hippocampus of aggressive rats was also studied, using a scintillation method. It has been found that the new peptide mimetics – M6 and P6, demonstrated different modulating effects on the exploratory behaviour and memory and on the 5-HT release in the hippocampus of grouped and socially-isolated male rats. The two compounds had different effects on the exploratory behaviour and the process of habituation in aggressive animals, probably due to their isomeric structure. M6 increased significantly the memory in grouped animals, but had the opposite effect in aggressive rats. Due to its intrinsic peptidomimetic nature, it is possible that M6 has an affinity towards 5-HT receptors in hippocampus.

Key words: peptidomimetics, memory, social isolation, serotonin, hippocampus

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THE INFLUENCE OF SOLVENTS ON THE MOLECULAR STRUCTURE AND BIOLOGICAL ACTIVITY OF N,N'-BIS(N-NICOTINOYL-L-VALYL)-DIAMINOHEXANE

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ABSTRACT

A peptidomimetic, N,N'-bis(N-nicotinoyl-L-valyl)-diaminohexane (M6) dissolved in identical concentration in three different types of solvent - sunflower oil, water and dimethyl sulfoxide (DMSO) was used for in vivo experiments with rats. Water and oil solutions did not provoke any symptoms of intoxication, while gross renal and hepatic toxicity was found when using DMSO solution. UV studies of M6 in several solvents, including water and DMSO showed solvatochromic shifts, due to intermolecular solvent-solute non-covalent interactions.

Keywords: solvatochromism, UV adsorption, peptidomimetic, toxicity.

PHARMACOLOGICAL MODULATION OF SEROTONIN LEVELS IN HIPPOCAMPUS OF SOCIALLY ISOLATED RATS

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Summary
Background: Social isolation can change the cognitive functions of animals and humans and lead to aggressive behaviour. The cognitive deficits characteristic of aggressive animals can be effectively modulated by newly synthesized peptidomimetics, derivatives of the natural essential amino acid L-Valine and niacin or its isomer - isonicotinic acid.
Methods: Experimental model of aggression induced by social isolation (over 6 weeks) in male Wistar rats was used to study some changes in cognitive functions. Treatment of rats (aggressive and grouped) with the peptidomimetic compounds was for three days, 100 mg/kg of body weight, intraperitoneally. The effect of new peptidomimetics on the cognitive functions of aggressive animals (learning and memory and exploratory behavior) was studied. Serotonin release and uptake in hippocampal tissue of treated animals were measured by radiolabeling methods after three days of administration of the compounds.
Results: It was found out that the two isomeric peptidomimetics (M6 and P6) modulated some memory functions (long-term memory and exploratory behavior). The two compounds altered significantly serotonin release and especially serotonin uptake in hippocampal tissue of aggressive animals in comparison to both grouped and aggressive control rats.
Conclusions: The newly synthesized peptidomimetics are effective modulators of aggressive behavior due to their possible affinity for serotonin receptors in hippocampus. Their influence on serotonin levels in the hippocampus of aggressive animals deserves further studies and the compounds promise future development as potential pharmacological agents.
List of Abbreviations: 5-HT (serotonin); M6 – peptidomimetic, derivative of L-valine and niacin; P6 – peptidomimetic, derivative of L-valine and isonicotinic acid; ANOVA – analysis of variance
Key words: hippocampus, aggression, cognition, peptidomimetics, serotonin

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Preliminary study on *in vivo* toxicity of monensin, salinomycin and their metal complexes

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The acute toxicity of the polyether ionophores monensin, salinomycin and their metal complexes with Na(I), Mg(II), Ca(II), Mn(II), Co(II), Zn(II) was evaluated in mice. The experimental data revealed that Ca(II) and Mg(II) complexes of salinomycin display the highest toxicity among the compounds tested, with LD_{50} values of 20.5 mg/kg b.w. (13 μmol/kg b.w.) and 25.8 mg/kg b.w. (17 μmol/kg b.w.), respectively. The preliminary evaluation of biochemical indices of survived animals showed that no significant changes occur within a three-day treatment with ionophorous antibiotics and their complexes.

Keywords: polyether ionophores, metal complexes, acute toxicity, biochemical indices

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A new approach for investigating neurodegenerative disorders in mice based on DSC

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Abstract In this work, we develop a new approach based on differential scanning calorimetry (DSC) for diagnostics and characterization of the changes in the brain at molecular and supramolecular level associated with drug-induced neurodegenerative disorders. In order to test the DSC potential, we used an experimental animal model of scopolamine-induced dementia of Alzheimer's disease (AD) type. The DSC measurements taken on supernatants of brain tissue homogenates isolated from healthy animals and animals with scopolamine-induced dementia showed that heat capacity curves for animals with scopolamine-induced dementia strongly differ from the respective curves for healthy animals. The effects of preventive treatments with various substances and their combinations expected to have protective effect and hinder the development of AD (myrtenal, ellagic acid, lipoic acid, ascorbic acid) are also clearly displayed in the calorimetric scans. These measurements show that DSC is an appropriate method for detection and characterization of the compositional changes taking place in affected by dementia brain tissues.

Keywords DSC · Scopolamine-induced dementia · Neurodegenerative disorder · Alzheimer's disease

Introduction

Differential scanning calorimetry (DSC) is a new, recently introduced method for diagnostics and monitoring of diseases as well as for obtaining information on the disease mechanisms at molecular level. DSC is a long known and widely used method in molecular and membrane biophysics studies, as well as in various other disciplines, but its high potential in medical research has only recently been recognized. Several publications from the recent years have demonstrated the DSC diagnostic potential in studies of biological fluids, in particular, blood plasma [1–9], serum [6, 10], synovial fluid [11], and cerebrospinal fluid [12]. DSC has also turned out to be a sensitive method for detection of changes in the protein profiles of body fluids resulting from brain tumors [12, 13].

The Alzheimer disease (AD), the most frequent form of dementia, is an important problem of modern society

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Comparative studies on two isomeric L-valine peptidomimetics for neuropharmacological effects in rodents

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It is well known that biological activity is a function of chemical structure of the compounds, and that positional isomers frequently differ in biological activity. Positional isomerism is a subtype of structural isomerism. Two new compounds which are isomeric peptide mimetics, derivatives of L-Valine, and contain hydrophobic spacers of six methylene groups and moieties of either nicotinic or isonicotinic acid were studied for their neurobiological effects in vivo.

Aim of the present study was to evaluate the neuropharmacological activity of these peptide mimetics on rodents with experimental model of social isolation. Male Albino ICR mice and Wistar rats, treated with effective daily doses in 3 consecutive days were used. Their cognitive functions (learning and memory - Step-through test, exploratory activity - Hole-board test) were evaluated. The effects of the compounds on release and reuptake of serotonin in hippocampus and on stimulated acetylcholine release also were studied in hippocampal slices of Wistar rats.

Our results revealed a significant dose-dependent effect of the positional isomers. They both modulated cognitive functions and changed the release of Serotonin (5-HT) and the reuptake of Acetylcholin (Ach) in brain differently. The CNS effects are most probably related to the presence of L-Valine and a hydrophobic spacer which increases liposolubility of the compounds. The main reason for differences in the modulating effect on cognitive functions of rodents, and upon neuromediator levels is most probably the positional isomerism of the nicotinic and isonicotinic residues.

Key words: isomeric peptidomimetics, L-valine, nicotinic and isonicotinic acid, memory, neuromediators

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Modulating effect of new neuropeptide on central nervous system and on dopamine neurotransmission in mice

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The neuropeptide with code P2 (Nociceptin analogue, modified in position 13 with unnatural amino acid canavanine, Cav) is object of present work. We investigated its central nervous system (CNS) activity and modulating effect on dopamine levels in mice brain. The substitution of Lys^{13} by Cav in the nociceptin molecule affects the selectivity of the peptide action. P2 has dose-dependent antinociceptive effect in mice and also changed some brain neuromediators via decrease of dopamine uptake. The synthesized nociceptin analogue has promising pharmacological effects on CNS.

Key words: neuropeptide, hexobarbital narcosis, nociception, dopamine uptake

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Effects of new neurotensin analogue on brain activity in rat Parkinson's disease model

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Parkinson's disease (PD) results in progressive loss of dopamine (DA) neurons and leads to motor disturbances. The close connection between DA-ergic neurotransmitter system and Neurotensin (NT) mediation was established which suggests that NT is associated with PD. It was reported that NT can modulate the activity of DA neurons. Our previous data demonstrated significant CNS-activity in rodents of some new NT-analogues. The aim of the present study was to evaluate the potential modulating effect of new NT-analogue on the behavior and brain activity in rats with model of PD which was induced in male Wistar rats via unilateral injections of 6-hydroxydopamine (6-OHDA) and verified by apomorphine test. Animals were treated 5 days with new NT analogue in effective doses after the induction of PD. Standard test was used for evaluation of neuro-muscular coordination (Rot-a-Rod). Electroencephalography (EEG) was used also to measure the brain activity in inactive condition. Experimental data were processed by Student-Fisher, or Mann-Whitney or Kruskal–Wallis test. Rot-a-rod test showed gradual improvement in the motor performance of NT-treated animals compared to control PD- rats with saline. In the same time EEG showed differences in spectral composition and patterns above the lesioned areas and their hemispheric counterparts in the PD-animals treated with NT-analogue compared to saline treated PD-rats and similarities with the healthy ones. In conclusion the new NT-analogue is promising anti-PD agent and deserves further investigations.

Keywords: Neurotensin, Parkinson's disease, 6-hydroxydopamine, Neuropeptides, EEG

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Low-temperature exothermic transitions in brain proteome of mice, effect of scopolamine

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ABSTRACT

Differential scanning calorimetry (DSC) has been employed to examine the thermal behavior of brain tissues affected by a drug-induced neurodegenerative disorder. An animal (mouse) model of scopolamine-induced dementia was used. The DSC measurements performed on supernatants of brain tissue homogenates revealed large differences between the heat capacity profiles for healthy animals and for animals with scopolamine-induced dementia. The heat capacity profiles of the supernatants from healthy animals displayed well expressed exothermic transitions peaking in the range 35–45 °C, thus preceding in temperature the endothermic denaturational transitions. No such exothermic transitions were found in other samples from the same animals, e.g., centrifugation sediments of brain homogenates, liver homogenates, blood plasma. Remarkably, the low-temperature exotherms were completely abolished by the scopolamine treatment. The exothermic events may possibly reflect a process of aggregation of specific protein fractions in the brain supernatants. The reported findings may be important for the elucidation of the molecular mechanisms of cognitive impairment.

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A novel DSC approach for evaluating protectant drugs efficacy against dementia

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Intrinsically disordered proteins

ABSTRACT

Differential scanning calorimetry was applied to evaluate the efficacy of preventive treatments with biologically active compounds of plant origin against neurodegenerative disorder in mice. As we reported recently, large differences exist between the heat capacity profiles of water-soluble brain proteome fractions from healthy animals and from animals with scopolamine-induced dementia: the profiles for healthy animals displayed well expressed exothermic event peaking at 40–45 °C, by few degrees above body temperature, but still preceding in temperature the proteome endothermic denaturational transitions; the low-temperature exotherm was completely abolished by the scopolamine treatment. Here we explored this signature difference in the heat capacity profiles to assess the efficacy of preventive treatments with protectant drugs anticipated to slow down or block progression of dementia (myrtenal, ellagic acid, lipoic acid and their combinations, including also ascorbic acid). We found that these neuroprotectants counteract the scopolamine effect and partially or completely preserve the 'healthy' thermogram, and specifically the low-temperature exotherm. These results well correlate with the changes in the cognitive functions of the animals assessed using the Step Through Test for learning and memory. The exothermic event is deemed to be associated with a reversible process of fibrillization and/or aggregation of specific water-soluble brain protein fractions preceding their denaturation. Most importantly, the results demonstrate that the effect of scopolamine and its prevention by protectant substances are clearly displayed in the heat capacity profiles of the brain proteome, thus identifying DSC as a powerful method in drug testing and discovery.

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New mechanisms in preventive effect of ellagic acid on cognition in mice with Alzheimer's disease type dementia

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Antioxidant mechanisms in protective effects of some natural compounds on progression of Alzheimer's disease (AD) were reported during last years. Our previous data revealed significant improving effect of a natural polyphenol Ellagic Acid (EA) on rodent cognitive functions. The goal of this study was to evaluate the effect of EA on cognition of mice with chemically induced dementia from AD type. This animal model was produced via Scopolamine treatment of male Albino mice and was verified by cognitive and biochemical methods. After 5-days treatment with EA both the changes in the cognitive functions of animals and biochemical correlates were evaluated. Significant preventive effect of EA on the processes of learning and memory (Step-through test) of dement animals was established. The high percent (50%) of memory prevention by EA was accompanied by significant antioxidant effect (decreased lipid peroxidation) and inhibited activity of acetylcholine esterase in the brains of EA-treated animals. An increase of dopamine uptake in the brains of EA-treated dement animals was also found. Our results reveal some of the complex mechanisms underlying the EA preventive effect on the cognition in mouse model of AD-dementia.

Key words: Ellagic acid, Alzheimer's disease, Memory, Antioxidants, Acetylcholine esterase, Dopamine

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Research Article Open Access

Proteomic Analyses of Exothermic Processes in Rat Brain Homogenate

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Abstract

Alzheimer's disease (AD) is the most widespread neurodegenerative disorder which can be induced by a scopolamine but the underlying molecular mechanism is poorly understood. Recently, differential scanning calorimetry (DSC) has been used in study healthy and scopolamine-treated mice. A well-expressed exothermic transition minimum in the range of 35 - 45°C was determined in the DSC profiles of healthy mice supernatants. To explain this process, using two-dimensional gel electrophoresis (2D-PAGE) coupled with MALDI-TOF-TOF, poorly soluble membrane proteins in hippocampal proteome of rat brain tissue were identified. The different behavior of the hippocampal proteome from the healthy rats before and after heating to 45°C was identified. Due to the demonstrated change in protein level of tau and tubulin in the rat hippocampus after heating to 45°C, it was suggested that the observed exothermic process at 35-45°C in rat may be due to the partial unfolding of tau protein, which leads to the release of tubulin. Both proteins together are involved in protein fibrillation and aggregation.

Another important result is the discovery of different profiles for the proteome of hippocampal rat homogenates with scopolamine-induced neurodegenerative disorder and its characteristics from healthy rats.

The reported results from this study can help clarify the molecular mechanisms of scopolamine-induced dementia and neurodegenerative processes in general.

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Antioxidant mechanisms in neuroprotective action of lipoic acid on learning and memory of rats with experimental dementia

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Alzheimer's disease (AD) is one of the most common dementia affecting about 36 million people and without effective cure. Oxidative stress is one of many hypotheses for the AD mechanisms. Possible preventive AD effects of some antioxidants continue to be the object of clinic and experimental research. The aim of this study was to evaluate the antioxidant mechanism in the neuroprotective effect of lipoic acid (LA) on the cognitive functions in experimental dementia. Alzheimer's disease type dementia was produced *via* scopolamine treatment (Sco, 1 mg/kg i.p., 11 days) on male Wistar rats. Lipoic acid (LA, 30 mg/kg, i.p.) was applied for the same period. Learning and memory performance of the rats were evaluated using passive avoidance learning test (Step through test). At the 24th hour after the last treatment the brain frontal cortex, hippocampus, and striatum were isolated and homogenized. The homogenates were used for determination of malondialdehyde (MDA), total glutathione (tGSH), and activities of superoxide dismutase (SOD), glutathione peroxidase and catalase (CAT). The dementia model was verified by the cognitive tests used. In brain structures of the Sco-group increased MDA, and decreased tGSH levels, as well as activated antioxidant enzymes were observed. LA significantly improved cognitive functions and oxidative status damaged by Sco by increased tGSH level, restored CAT and SOD activities. Thus LA significantly protects memory impairments of dement animals due to its antioxidant capacity and could be used in prevention and therapy of AD.

Key words: Alzheimer's disease, Lipoic Acid, Oxidative stress, Scopolamine

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Effect of *Melissa officinalis* L. on the level of induced lipid peroxidation in mouse liver

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The aim of this study was to evaluate the effect of *Melissa officinalis* L. aqueous extract on the level of induced lipid peroxidation in mouse liver homogenate. Samples were prepared from homogenized BALB/c mice liver, and subsequently incubated with one of the following lipid peroxidation inducing agents: 0.5 mM H_2O_2; 0.1 mM $FeCl_3$ +ascorbate or H_2O_2 +$FeCl_3$+ascorbate (Fenton reaction), in the presence or absence of extract. *M. officinalis* aqueous extract was prepared by extraction with boiling deionized water in 1:10 ratio (w/v). In the experiments were used two-fold dilutions of the extract containing phenolics equivalent of 21.4 to 1.32 mg gallic acid following preliminary determination of the total phenolic content by Folin-Ciocalteu assay. The levels of lipid peroxidation in mouse liver homogenate, caused by all of the oxidative agents were significantly reduced by all tested dilutions of the extract. *M. officinalis* aqueous extracts could be effective for protection of liver cells from induced lipid peroxidation.

Keywords: Phenols, Mice, Antioxidant, Aqueous extract, *M. officinalis*

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Preventive Effect of Two New Neurotensin Analogues on Parkinson's Disease Rat Model

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Abstract

Close functional and anatomical interactions between the neurotensin (NT) and dopamine (DA) systems suggest that NT could be associated with Parkinson's Disease (PD). However, clinical use of NT is limited due to its rapid degradation. This has led to the synthesis of a number of new NT fragment 8-13 [NT(8-13)] analogues, such as NT2 and NT4, to avoid the fast biodegradation of NT. The aim of this study was to investigate the neuroprotective effects of NT2 and NT4 on an experimental model of Parkinson's disease in rats induced with 6-hydroxydopamine (6-OHDA) treatment, producing striatal lesions. Wistar male rats were divided into different groups: a sham-operated (SO) group, a striatal 6-OHDA-lesioned control group, two groups of 6-OHDA-lesioned rats treated for 5 days with NT2 or NT4 (10 mg/kg, intraperitoneally) and a NT-treated group as reference. During the first and second week post lesion the animals were subjected to a number of behavioral tests (apomorphine-induced rotations, rotarod, passive avoidance test), and brain tissue was evaluated histologically and also assessed for DA levels. The results showed that both the number of apomorphine-induced rotations and falls (rotarod test) increased in the 6-OHDA group relative to the SO group. At the same time, the 6-OHDA-treated group showed significant memory impairment, based on the to step-through test, compared to the SO group. Treatment with NT2 and NT4 significantly decreased the number of apomorphine-induced rotations and improved the memory of lesioned animals, with these NT analogues demonstrating better neuroprotective and neuromodulatory effects than NT. DA content in the brain of the PD rats treated with NT2 and NT4 increased, possibly due to attenuation of the loss of DA-ergic neurons. NT2 and NT4 were found to easily penetrate the blood–brain barrier and they showed a better stability than the reference NT neuropeptide. In conclusion, the NT approach represents an attractive strategy for the treatment of neurodegenerative disease.

Keywords 6-OHDA · Parkinson's disease · Neurotensin · Neuroprotection · Neuropeptides

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Original article

ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY OF MONOTERPENOID MYRTENAL IN RODENTS

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ABSTRACT

Inflammation and pain are common phenomena associated with a number of diseases. The search for new pharmacological agents is an important factor in delivering better therapy. Many plants and their active ingredients monoterpenes exhibit analgesic and anti-inflammatory activity but have not been fully studied.

Purpose The bicyclic monoterpenoid Myrtenal (M) is a component of many plants essential oils. Researches on total plant extracts as well as on essential oils reveal a wide range of biological effects with various mechanisms. However, there is no data in the literature about Myrtenal effects in pain and inflammation. Aim of this study is to investigate the M effects in models of pain and inflammation in laboratory rodents.

Materials and methods Anti-nociceptive activity of M (30 mg/kg, b. wt., i. p.) was tested in male ICR mice after single and repeated administration on two established experimental pain models - Acetic acid writhing test (antipyretic type analgesia) and Hot plate test (narcotic type analgesia). Anti-inflammatory activity of M (40 mg/kg, b. wt., i. p.) was evaluated on the 24th h from the last treatment after 5-d administration via carrageenan-induced inflammation model on rat paw and was compared with this of the non-steroid anti-inflammatory drug (NSAID) Ketoprofen (2.5 mg/kg, b. wt., i. p.) as a referent.

Results In our experiments on Wistar rats and ICR mice M demonstrated significant anti-inflammatory and anti-nociceptive properties (toward both peripheral and thermal pain). In acute administration, significantly decreased the abdominal writhing number at 15th ($p < 0.01$) and 20th min ($p < 0.05$) by 47.25 % and by 50.55 % respectively. Myrtenal decreased ($p < 0.001$) the number of jumps versus control group after repeated treatment – by 40.4 % on 7th and by 43.1 % on the 14th d in comparison to the controls.

Conclusions Possible mechanisms are complex, and they probably include sedative and antioxidant properties of Myrtenal.

Keywords: Myrtenal, anti-nociceptive, anti-inflammatory effects, rodents

INTRODUCTION

Terpenes form the basic skeleton of many plant-derived biologically active substances as glycosides, saponins, alkaloids, vitamins and others. The substances from this large group exhibit a wide range of biological activities in cancers, malaria, inflammatory processes, and infectious (viral and bacterial) diseases [1].

Low-molecular monoterpenes, which are a basic component of essential oils, are of great interest to scientific circles. Monoterpenes as secondary plant metabolites have been shown to exert antimicrobial, antiviral, anti-atherosclerosis, cardioprotective, antiulcerogenic, cytotoxic, antineoplastic, mutagenic, antidiabetic, anti-inflammatory, antioxidant, anti-aging, antihepatotoxic, antihypertensive, hypolipidaemic and antiplatelet activities.

The role of inflammation in the pathogenesis of many diseases is known. These conditions are accompanied by different pain manifestations. Monoterpenes successfully affect inflammation [2] and chronic pain [3]. Many plant essential oils rich in monoterpenes exhibit experimental pain-relieving effects [4]. The anti-inflammatory activity of pinene has been established [5] as well as its anti-nociceptive activity [6]. Myrtenol is a mono-oxidized isomer of pinene, which also exhibits anti-inflammatory properties combined with analgesic activity [7].

A representative of monoterpenes Myrtenal is a bicyclic derivative of α-pinene ((“)-Myrtenal, (1R)-2-Pinen-10-al, (1R)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-carboxaldehyde) (Fig. 1).

A REVIEW: BIOLOGICAL ACTIVITY OF MYRTENAL AND SOME MYRTENAL-CONTAINING MEDICINAL PLANT ESSENTIAL OILS

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ABSTRACT

INTRODUCTION: Myrtenal, a component of many plants' essential oils, is a bicyclic monoterpenoid. Numerous effects of myrtenal in experimental animals have been found – bronchodilatory, anti-inflammatory, anti-aggregative and antihemolytic (*in vitro*), and antibacterial. Its other activities have been studied – antioxidant, antitumor, antihyperglycemic, vasodilating, heart rate reducing and hypotensive. Myrtenal is relatively little studied in the field of neuroscience.

AIM: The aim of this article is to summarize the available information on the established biological activity of the monoterpenoid myrtenal.

MATERIALS AND METHODS: Scientific databases such as PubMed, ResearchGate, HMDB and others have been used to provide information on the published results of properties and activities of the test substance (myrtenal) over a period of 15 years (2003 – 2018).

RESULTS: Our research confirmed the available data for its central nervous system (CNS) activity – anxiolytic and potentiating the effects of the hypnotic drugs, as well as the antioxidant properties. We have evaluated the neuromodulatory activity of M in brain tissue manifested in elevated levels of major neurotransmitters in healthy rodents and those with neurodegenerative changes accompanied by improvement in the animals' memory.

CONCLUSION: Significant protective effects of myrtenal on neurodegenerative processes were established. Probably they are related to its complex mechanisms, including neuromodulatory and antioxidant properties.

Keywords: *myrtenal, biological activity, neurodegeneration*

molecules

MDPI

Article

Curcumin: Total-Scale Analysis of the Scientific Literature

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Abstract: The current study aimed to provide a comprehensive bibliometric overview of the literature on curcumin, complementing the previous reviews and meta-analyses on its potential health benefits.

Bibliometric data for the current analysis were extracted from the Web of Science Core Collection database, using the search string TOPIC=("curcumin*"), and analyzed by the VOSviewer software. The search yielded 18,036 manuscripts. The ratio of original articles to reviews was 10.4:1. More than half of the papers have been published since 2014. The major contributing countries were the United States, China, India, Japan, and South Korea. These publications were mainly published in journals representing the following scientific disciplines: biochemistry, chemistry, oncology, and pharmacology. There was a significant positive correlation between the total publication count and averaged citations per manuscript for affiliations, but not for countries/regions and journals. Chemicals that were frequently mentioned in the keywords of evaluated curcumin publications included curcuminoids, resveratrol, chitosan, flavonoids, quercetin, and polyphenols. The literature mainly focused on curcumin's effects against cancer, inflammation, and oxidative stress. Cancer types most frequently investigated were breast, colon, colorectal, pancreatic, and prostate cancers.

Keywords: curcumin; pharmacology; bibliometrics; biochemistry; cancer; citation analysis; VOSviewer; Web of Science

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To whom it may concern

The Editorial Board of the *Journal of Chemical Technology and Metallurgy* certifies that the manuscript titled

ACTIV L-VALINE PEPTIDOMETRIC: SYNTHESIS AND NEUROPHARMACOLOGIVAL EFFECTS

submitted by: Eleonora N. Encheva, Daniela S. Tsekova, Yordan K. Hodzhev, Hristina H. Nocheva, Lyubka P. Tancheva

is accepted for publication.

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Prof. Dr. Bogdana Koumanova

Editor-in-Chief

Active L- Valine peptidomimetic: synthesis and neuropharmacological effects

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Abstract

Introduction: It is widely accepted that social isolation stress affects neurodevelopment negatively, but sexual differences have not been clarified in detail. The purpose of the study was to examine existence of sexual dimorphism in memory, balance and exploratory behavior in adolescent male and female rats with parental deprivation, and to compare the results of the study with socially isolated adolescent rats of both sexes.

Methods: Post weaning social isolation (21st PND) of 6 male and 6 female Wistar rat pups over a period of 6 weeks was used as a method of chronic stress. Another set of two groups of male and female pups were raised in 2 separate cages (6 animals per group, of the same sex) again for the same period as the socially isolated young rats. At the end of this period the animals were introduced to the behavioral panel of tests: Rotarod test, Hole board test, and Step-through test. The rats were tested for memory retention one hour after acquaintance of the animal with the test, and 24 hours later. We used ANOVA (mixed design) to compare and analyze the results.

Results: Male socially isolated rats scored persistently lower compared to male grouped animals in the Rotarod test. They also scored lower compared to female isolated rats. The latter endured longer on the Rotarod compared to grouped female rats.

Male socially isolated rats exhibited a much stronger rise in exploratory behavior on the Hole-board compared to female socially isolated rats in comparison with their grouped counterparts. Sexual differences were also observed in memory retention tested with the Step-through.

Discussion and conclusions: Our results demonstrate for the first time that memory and neuro-muscular coordination of rats in their adolescent period are differently influenced by chronic stress depending on sex of animals and on severity of the isolation stress.

Keywords: social isolation, adolescent period, sexual differences

Chapter 34

In Vitro and in Vivo Studies on Toxicity and Pharmacological Activity of New L-Valine Peptidomimetics

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Abstract - Four newly synthesized peptidomimetics were studied as potential pharmacological agents. The aminoacid L-valine is bound to nicotinic (m-pyridinic) acid – [***M***] or isonicotinic (p-pyridinic) acid [***P***] on one side, and to alkyl spacer containing 3 or 6 methylene groups on the other side. Our results show that the compounds are neuropharmacologically active agents (especially 6 - isomers) with low toxicity (in vivo and in vitro) and moderate antiviral activity against Herpes Simplex. The compounds showed a very low toxicity in vivo (in Albino mice) (intraperitoneal and oral- over 2 000 mg/kg, and cytotoxicity lower than this of vitamin C) and also in vitro (in cell culture); as well as a good therapeutic index (over 8). Established antiviral activity against herpes simplex was moderate and is probably related to their chelating activity. Two of compounds (***M6*** and ***P6***) increased processes of learning and memory in mice and had significant analgesic effect. Their high lipid solubility is probably responsible for their CNS-affinity. ***M6*** and ***P6*** had a higher log P than ***M3*** and ***P3*** (in system octanol/water) and they had better analgesic and anticonvulsant activity in vivo than compounds with 3 spacers. The compounds had the ability to modify the effects of some CNS-drugs. In acute treatment hexobarbital narcosis was prolonged by ***P6*** and ***M6***, but after 5 days of treatment they shortened it significantly. The mechanism of interaction is probably not only on the CNS level, but on the metabolic level too (affecting hepatic P-450- monooxygenases). The differences and varieties in their effects obviously are due to their positional and structure isomery.

Keywords - L-valine, peptidomimetics, toxicity, biological activity, cognitive enhancing drugs, drug development

Chapter 33

Protective Effect of New L-Valine Derivatives on Brain Function in Experimental Model of Aggression in Mice after Social Isolation

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Abstract - Two newly synthesized compounds combine amino acid L-valine and pyridinic moiety attached in *m-(**M**)* or *p-(**P**)* positions. Previous data demonstrated their low toxicity and good therapeutic index. The purpose of this study is to evaluate their influence on the cognitive processes on the model of experimental aggression in mice by social isolation (for period of 6 weeks). Applied in Albino mice (125 mg/kg b.w. i.p., for 3 days) both compounds improved significantly short-term and long-term memory (step-through test) (about 50%) as well as exploratory activity. Neuromuscular coordination and muscle tone were significantly increased by ***M-6***, and even better by ***P-6***. Compound ***P-6*** has significant analgesic effect according acetic acid test. Isolated mice were divided in two groups - aggressive and non-aggressive animals. Surprisingly, isolated non-aggressive animals had even better short-term and long-term memory than control animals living in a group. Aggressive mice demonstrated bad cognitive functions. Both compounds increased significantly damaged long-term memory in aggressive animals (***M-6*** with 81% and ***P-6*** with 88%) as well as exploratory activity, muscle coordination, stability and concentration of animals. The improving effect of ***M-6*** and ***P-6*** on the cognitive functions of control mice living in groups was commensurate with that of isolated aggressive animals. The mechanism of the stable preventive effect of both compounds on damaged cognitive processes in aggressive animals is still not clear. The variations in the effects of both compounds can be explained with their positional isomery and difference in some physico-chemical parameters.

Keywords - L-valine, aggression, animal models, learning and memory

Introduction

Effective protection with amino acids and pyridine derivatives has been reported against memory deficit occuring in some mental diseases, aggression, trauma, brain

Chapter 36

Learning, Memory and Biogenic Amine Levels in Rat Hippocampus after Treatment with New L-Valine Derivatives

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Abstract - Memory deficit was documented after brain damages, trauma, intoxications or diseases and aging. Improving effect of some amino acids and nicotinic acid derivatives had been reported in literature.

Two newly synthesized compounds combine in their molecule the amino acid L-Valine and nicotinic or isonicotinic acid. They differ in structures only by the position of L-Valine connected by amide bonds to a pyridine residue in *m*-(M) or *p*-(P).

The compounds (in repeated doses 125 and 250 mg/kg b.wt. i.p. for 3 days) M6 and P6 demonstrated significant neuropharmacological activity on learning and memory in experiments with Albino mice (step through test), exploratory activity (hole board test) and nociception (acetic acid test). The established effects were stable and persisted even after 7 days after treatment.

Some differences in biogenic monoamine levels in hippocampus were examined in male Wistar rates treated with a single dose of the compounds (250 mg/kg, b.wt. i.p). In comparison to the control animals the levels of 5-hydroxytriptamine and noradrenaline were significantly increased by P-6.

Our results show that the compounds are pharmacological active agents improving learning and memory and changing the functional activity of neurotransmitter system in rat hippocampus. They can modulate levels of biogenic amines probably via regulation of release of dopamine, noradrenaline and serotonin.

Keywords - learning, memory, biogenic monoamines, hippocampus, L-valine

Introduction

Memory deficits were documented after brain damage, trauma, intoxications or neurological alterations and aging. Two newly synthesized compounds combine in their molecule amino acid L-valine and nicotinic or isonicotinic acid (1, 2). They differ in structures only by the position of L-valine connected by amide bonds to a pyridine residue in *m*-(***M***) or *p*-(***P***) position.

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Biological properties of copper(II) complexes of the macrolide antibiotic Tylosin

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ABSTRACT

Macrolide antibiotic Tylosin (HL) binds copper(II) ions to form two type of complexes depending on reaction conditions. Mononuclear violet complex **1** [CuL_2] consists of metal(II) ion placed in a square-planar environment where Tylosin monoanions act in a bidentate coordination manner *via* amino- and deprotonated OH-groups. At comparable metal-to-ligand molar ratio Tylosin forms binuclear complexes of composition [$Cu_2L_2X_2$] (X = Cl^- (**2**) or NO_3^- (**3**)). The copper(II) centers are four-coordinated by two oxygens from two ligand anions, one Tylosin nitrogen atom and one inorganic anion. Tylosin serves as a bridge between both metal ions through its oxygen atom from deprotonated hydroxyl moiety and acts in a bidentate mode.

The biological assays revealed that Tylosin and its complexes are relatively non-toxic compounds (white male ICR mice). The *in vitro* determined antibacterial and SOD-like activities showed that copper(II) complexes **1-3** are generally more promising agents than the non-coordinated Tylosin base.

НОЦИЦЕПТИН И ПИЛОТНИ ОПИТИ ЗА ОТКРИВАНЕ ФАРМАКОЛОГИЧНИ ЕФЕКТИ НА НЕГОВИ КЪСОВЕРИЖНИ АНАЛОЗИ

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NOCICEPTIN AND PILOT EXPERIMENTS TO DETECT PHARMACOLOGICAL EFFECTS OF ITS SHORT-CHAIN ANALOGUES

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РЕЗЮМЕ

Ноцицептин (орфанин) е ендогенен лиганд, свързващ се с ноцицептинов рецептор (NOP, ORL-1). Той притежава антианалгетични ефекти. Рецепторът е широко експресиран в мозъчните структури. Пептидомиметиците са молекули с къса верига, наподобяващи пептиди, с характерни фармакокинетични свойства. Целта на изследването е да се проучат основните фармакологични и токсикологични ефекти на два новосинтезирани пептида (P1 и P2) при мишки. Анализирана беше активността им върху ЦНС, както и влиянието им върху хексобарбиталов сън. Аналгетичната активност на двете вещества беше изследвана с тест с оцетна киселина. По същия метод бе проучен и дозо-зависимият ефект на аналгетичната активност на P2. Установи се, че P2 притежава антиноцицептивни свойства, което го прави подходящ за по-нататъшни проучвания в тази насока.

Ключови думи: *ноцицептин, аналози, пептидомиметици, хексобарбитал, наркоза*

ABSTRACT

Nociceptin, or orphanin FQ, is an endogenous ligand for the nociceptin receptor (NOP, ORL-1). It is a potent antianalgesic agent. The receptor is widely distributed in brain structures. Peptidomimetics are short-chain molecules designed to mimic peptides and with typical pharmacokinetic properties. The aim of the study is to investigate the basic pharmacological and toxicological effects of two newly-synthesized neuropeptides (P1 and P2) in mice. Their activity on the CNS and their influence on the hexobarbital-induced narcosis as well were studied. The analgesic activity of these two compounds was examined by using acetic acid test. Dose-dependent effect of the analgesic activity of compound P2 was independently studied by means of the same method. It was established that P2 possessed antinociceptive properties which makes it suitable for further research in this direction.

Key words: *nociceptin, analogues, peptidomimetics, hexobarbital, narcosis*

Chapter 37

Pilot studies of pharmacological and toxicological effects of newly synthesized neuropeptides with short chains

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Abstract. Two new short-chain neuropeptides, synthesized by T. Pajpanova, (2013), analogues of Tyr- MIF 1 and nociceptine are object of this research. The aim of the study is to investigate the basic pharmacological and toxicological effects of two new neuropeptides (P1 and P2) on laboratory rodents. Methods: Some basic toxicological characteristics of neuropeptides applied on Albino male ICR mice in several doses (5, 10, 20 and 50 mg/kg b. wt. i.p.) were studied. Their activity on the CNS was studied as well as their influence on the hexobarbital sleeping time (HB 100 mg/kg b. wt. i.p.). We studied the influence of the two compounds on the nocieception in mice (test with acetic acid) when effective doses (4, 8 and 16 mg/kg b. wt. i.p.) were applied. Results: The newly synthesized neuropeptides demonstrated several suppressive effects on the CNS when a dose of 50 mg/kg b. wt. was applied, which disappeared within 48 hours. There was no mortality after the acute treatment both on the 48th hour (acute toxicity) and on the 5th day (prolonged toxicity). Pathological changes in the internal organs of treated animals were not found. P1 and P2 have similar effects on HB narcosis (P1 shortens it by 40%, and P2 by over 50%), but the mechanism is unknown. It is possible that the substances accelerate the elimination of HB or have modulating CNS effect related to their neuropeptidic nature. On the other hand the compounds had different effects on the nocieception - P1 increases it (by 262%) and P2 has significant analgesic effect (by over 25%). The analgesic effect of P2 is dose-dependent. We suggest that it is related to its nociceptine structure and due to possible interaction with CNS receptors.

Key words: toxicity, neuropeptides, hexobarbital, nocieception

Chapter 45

Effect of Solvents on the Toxicity of Some L-Valine Peptidomimetics in Rats

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Abstract. The effect of solvent on the toxicity of drugs and pharmacological agents is extremely relevant in the medical and pharmaceutical practice Two newly synthesized peptidomimetics derived from the amino acid L-valine exhibited significant CNS pharmacological activity.
Aim of this study is to compare the effects of some commonly used solvents (water, sunflower oil and Dimethyl sulfoxide (DMSO) on main toxic biochemical and histological parameters of laboratory rodents after 3-days of treatment with effective doses of the newly synthesized compounds.
Methods: The experiments were conducted on mature male Wistar rats. The compounds with codes M6 and P6 (150 mg/kg, intraperitoneally, for 3 days) were dissolved in equal concentration in three different types of solvent - oil solution (sunflower oil), water (gum arabic) and an organic solvent, DMSO. Main biochemical parameters of toxicity in urine and histological samples of liver and kidneys were tested on day 4.
Results: In oil solution and aqueous suspension, the compounds do not cause significant changes in the studied biochemical urine parameters as well as in the hepatic and renal parenchymal histology. In contrast, dissolved in DMSO compounds demonstrated significant hepatic and renal toxicity comparable for both studied compounds, and accompanied by some biochemical changes in the urine. The control group of animals treated only with DMSO had no significant histological and biochemical urinary changes, demonstrating that the negative effect observed is not the result of solvent toxicity.
Conclusion: Increased toxicity of newly synthesized compounds dissolved in DMSO happens under an unknown mechanism. It is probably due to improved solubility and facilitated penetration of M6 and P6 through membranes, as well as to other pharmacokinetic changes produced by DMSO. An important interaction solvent-compound is also possible to have occurred on the level of hepatic drug metabolism. This suggestion is supported by the established significant parenchymal changes in the liver.

Key words.learning, memory, biogenic monoamines, hippocampus, L-valine

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ИЗСЛЕДВАНЕ ЧРЕЗ ДИФЕРЕНЦИАЛНА СКАНИРАЩА КАЛОРИМЕТРИЯ НА ЕФЕКТА НА МИРТЕНАЛ ПРОТИВ СКОПОЛАМИН-ИНДУЦИРАНА ДЕМЕНЦИЯ ПРИ ГРИЗАЧИ

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DIFFERENTIAL SCANNING CALORIMETRY INVESTIGATION OF DRUG EFFICACY OF MYRTENAL AGAINST SCOPOLAMINE-INDUCED DEMENTIA IN RODENTS

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ABSTRACT

In this study, we employed differential scanning calorimetry (DSC) to characterize the changes in the denaturational profiles of the brain proteome of mice associated with scopolamine-induced cognitive neurodegenerative disorder (dementia) induced by Scopolamine (Sc) and to evaluate the efficacy of a preventive treatment with Myrtenal (Myr), a natural product of plant origin expected to hinder dementia development. The DSC measurements performed on supernatants of brain tissue homogenates revealed large differences between the heat capacity profiles for healthy animals and for animals with scopolamine-induced dementia. The heat capacity profiles of brain tissue supernatants from healthy animals displayed well expressed low-temperature exothermic

transitions peaking in the range 35-45°C, thus preceding in temperature the endothermic denaturational transitions. The exothermic transitions were only observed in supernatants of brain tissue homogenates, and not in other samples from the same animals, e.g., centrifugation sediments of brain tissue homogenates, liver homogenates, blood plasma. Remarkably, the low-temperature exotherms were completely eliminated by the scopolamine treatment and replaced with high-temperature exothermic transitions. A most notable result of this study was that treatment with Myr applied simultaneously with the Sc treatment, neutralized the Sc effect and resulted in preservation of the low-temperature exothermic transitions. In principle, exothermic transitions might result from processes of protein aggregation or fibrillization, or from reversal of protein cold denaturation processes. The enthalpy (area) of the exothermic transitions is similar in magnitude to that of the endothermic denaturational transitions, thus suggesting that a substantial portion of the brain proteins was involved in the exothermic processes. These experiments demonstrated that DSC is an appropriate method with great potential for detection and characterization of brain proteome changes taking place in brain tissues affected by neurodegeneration.

Key words: DSC, dementia, myrtenal