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COUPLING BETWEEN SLOW WAVES AND SLEEP SPINDLES DURING SLOW WAVE SLEEP IN HUMANS DEPENDS ON FUNCTIONAL BRAIN STATES BEFORE SLEEP

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BACKGROUND. Slow wave activity (SWA) and sleep spindles are fundamental electrophysiological signatures of non-rapid eye movement (NREM) sleep in both humans and animals. Previous observations have revealed that these two sleep events are not independent during thalamo-cortical interactions. Furthermore, co-existent sleep spindles and slow waves have been viewed as a mechanism for offline information processing.

OBJECTIVE. The aim was to test the hypothesis that the coupling between SWA and sleep spindles is associated with offline learning during sleep. For this aim, we explored if the temporal synchronization between slow waves and spindle activity during slow wave sleep (SWS) in humans was modulated by preceding brain states, i.e., by functional activations induced by pre-sleep learning.

METHODS. We activated differentially the left and right hemisphere before sleep by using a lateralized variant of serial response time task (SRTT) and verified these inter-hemispheric differences by analyzing alpha and beta electroencephalographic (EEG) activities during learning. A total of 53 subjects were studied, with half of them training the right hemisphere, and the other half training the left hemisphere before sleep. The stability and timing of coupling between positive and negative phases of slow waves and sleep spindle activity during SWS were quantified at multiple electrode locations before during sleep.

RESULTS. Spindle activity was temporally synchronized with both positive (up-state) and negative (down-state) slow half waves. Synchronization of only the fast spindle activity was laterally asymmetric after learning, corresponding to hemisphere-specific activations before sleep. However, the down state was associated with decoupling, whereas the up-state was associated with increased coupling of fast spindle activity over the pre-activated hemisphere.

CONCLUSION. These observations provide original evidence that (1) the temporal grouping of fast spindles by slow waves is a dynamic property of human SWS modulated by functional pre-sleep activation patterns, and (2) fast spindles synchronized by slow waves are functionally distinct.

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TRANSLATION INVARIANCE OF VISUAL OBJECT RECOGNITION

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An important characteristic of visual perception is its degree of robustness to spatial transformations of the retinal image. For example, during object recognition, the visual system has to establish the identity of an object when it is projected to varying retinal positions - a capacity known as ‘translation invariance’ or ‘translation tolerance’. Previous attempts to assess the translation invariance of biological vision have produced controversial results. In this work, I will present the findings of a series of behavioural studies with human subjects showing that the objects trained at one retinal location can be recognized at high accuracy rates following translations up to 18 visual degrees. Computational modelling with deep convolutional neural networks also demonstrates extreme translation invariance and highlights some of the mechanisms which may underlie this phenomenon.

MOTOR THETA OSCILLATIONS IN AGING

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BACKGROUND. It has been suggested that a distributed oscillatory system in the brain operating in the theta frequency range plays a major role in coordinating motor actions. In this distributed theta system, a central coordinating (“hubbing”) function has been attributed to the medial frontal regions including the supplementary motor area (SMA) and the anterior cingulate cortex (ACC). Also, theta activity at motor cortical regions is closely associated with medial frontal theta activity, possibly in relation with movement regulation, monitoring and control. Aging-related alterations have been demonstrated for medial frontal theta activity, but it remains not well understood if theta oscillations at motor cortical regions change with advancing age in humans.

OBJECTIVE. In the present study, electroencephalographic (EEG) theta (3.5-7 Hz) oscillations were analyzed during motor response generation. The major objective was to explore the effects of human aging on the neurodynamics of motor-related EEG theta activity in sensorimotor tasks. EEG theta oscillations were targeted for analysis during motor response generation.

METHODS. Response-related potentials of young and older adults elicited in auditory and visual four-choice sensorimotor tasks were analyzed in the time-frequency domain. The phase-locking factor and total power were computed at motor cortical regions contra- and ipsilateral to the movement and at the midline to reflect phase synchronization and power of motor theta oscillations.

RESULTS. Major results demonstrated that in both young and older adults, a pronounced response-locked theta activity (3.5-7 Hz) was generated at premotor, motor and sensorimotor cortical regions contra-lateral to the responding hand. Aging was associated with a decreased lateral asymmetry in the phase synchronization of only the left-hand responses. Also, there was a strong aging-related suppression of theta power at the medial fronto-central region that was specifically enhanced and correlated with response speed only in young adults.

CONCLUSIONS. These results confirm the involvement of theta oscillations in movement generation in relation to action coordination in humans. Also, they show that aging is associated with a dysfunction of the oscillatory theta system for motor action regulation due to a strong suppression of a medial frontal integrating mechanism and an impaired balance in the functional control of responses with the right and the left hand.

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THE STRESS OF COVID-19 AND THE DEVELOPMENT OF FEARS

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A pandemic of COVID-19 has caused a surge in stress experienced by individuals around the world. This fact has given rise to a number of psychological, neuro-behavioral and clinical studies. It has been recognized that much of society's behavioral and emotional responses to the virus can be viewed in the context of the two main fears - fear of disease (nosophobia) and fear of death (thanatophobia). The assumption that poor mental health may increase susceptibility to infection and transmission of the virus during a pandemic has initiated a number of studies worldwide related to the psychological and physiological components of the disease and related underlying fears. Accordingly, theories about the main fears and the reasons for their emergence have been forwarded. It is argued that an increase in the manifestation of post-traumatic stress leads to increased fear of death, which in some cases further results in personality dysfunction. In view of this etiologic frame, it is proposed to emphasize on stress prevention and those post-stress programs that deal with fears. It is assumed that these focused programs would best manage the mental well-being of individuals. Further research is essential to examine the correlation between mental well-being, the course of the pandemic itself and each country's capacity to counteract it.

EFFECTS OF AGE AND CUE NUMBER IN ARBITRARY CLASSIFICATION TASKS

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Humans often classify objects and events in different categories in everyday life. The category learning process requires acquiring the characteristics (cues) of the category members and learning the associations between the stimuli and the responses in repeated presentation trial by trial.

We aimed to investigate the effects of age and the cue number in classification rules on category learning with arbitrary associated stimuli and responses.

The stimuli consisted of randomly distributed elements (blue, red, yellow, and green spheres or cubes) forming two types of dynamic patterns (“wall” and “cloud”) that moved either to the left, to the right, forward, or backward. Thus the stimuli differed by four characteristics: color, motion type, motion direction, and shape of the elements. We performed three category learning experiments which varied by the number of the cues defining classification rules used to separate the stimuli into two categories: in Experiment 1, the classification is determined by the color of the elements, in Experiment 2 - by the combination of direction and type of motion, and in Experiment 3 - by the combination of color, direction, and type of motion. In all experiments, the shape of the elements was irrelevant to the category learning task. Two age groups - 16 young (Md = 22 years) and 17 old (Md=67 years) observers participated in the experiments.

The results show that the response time differs non-significantly between the two age groups. For the elderly group, neither the classification rule nor the trial number affects the response time. For the young group, the response time increases with the cue number and decreases with the number of stimulus presentations. However, the decrease is slighter for classification by motion direction and type.

The proportion of correct responses depends on the participant group – the elderly group is less accurate. It varies with the number of cues being least for the combined rule. The performance improves with the trial number differently for the two age groups. The elderly group gives less correct responses than the young one when classifying stimuli differing by color or movement. In contrast, the proportion of correct responses is about the same for the combined rule.

The differences in the two age groups’ performances are probably due to the changes in working memory with age and the ability to ignore irrelevant information.

COMPARISON OF BASIC VISUAL FUNCTIONS BETWEEN CHILDREN AND ADOLESCENTS WITH DEVELOPMENTAL DISORDERS AND TYPICAL DEVELOPMENT

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Developmental disorders such as Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and Developmental Dyslexia (DD) are distinguished by a specific pattern of behavioural and learning difficulties with different core defining features. However, they also share some common deficits in sensory information processing. In order to better understand visual perception peculiarities in these disorders, we compared their results on standardized visual tests assessing basic visual functions like visual acuity, contrast sensitivity, colour vision, and stereo vision. One hundred twelve children and adolescents (8-16 years old, 75 boys and 37 girls) separated into four groups with ASD, ADHD, DD, or typical development (TD) participated in the study. All of the tests were performed while the participants wore their lenses or glasses if they already had a refractive error correction.

The results obtained showed similar results between all the groups participating in the study concerning the near visual acuity, stereo acuity, and colour vision anomalies. However, it was observed that a significantly higher number of participants in the groups with ASD and DD have lowered far visual acuity and decreased contrast sensitivity.

The impaired vision in the groups with ASD and DD could predetermine some of their difficulties in learning and education as well as daily activities and communication problems. Moreover, the diminished contrast sensitivity could potentially be associated with the compromised excitation/inhibition balance reported in ASD (and assumed in DD) and would influence the receptive fields' center/periphery relations.

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FIXATION STABILITY AND GAZE ALLOCATION AREA REFLECT DIFFERENCES AMONG ASD, ADHD, AND DD GROUPS ACCORDING TO THE TASK REQUIREMENTS

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Developmental disorders, like Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and Developmental Dyslexia (DD), have different

diagnostic features, but all of them have an atypical visual perception and eye movements. In the present study, we examined the fixation stability of gaze in children and adolescents from these groups and a group with typical development (TD) in a contour integration task. Sixteen participants from each group (64 in total) took part in the study. They had to detect a straight contour consisting of aligned Gabor patches placed amongst similar Gabor elements with random orientation. We varied the degree of elements' deviation from the contour (visual noise level) in separate blocks. The gaze position of the participants during the fixation point presentation preceding the stimulus was recorded and analyzed. The eye positions in this interval provide a measure of fixation stability and the ability of the participants to allocate gaze to the most informative parts of the subsequent stimulus presentation.

The eye positions were analyzed by spatial point analysis in which the points patterns were described as a realization of an inhomogeneous Poisson process. It allows estimating the differences in the area occupied by the gaze locations and the effect of the group differences and the noise level on it.

The results show that the gaze positions of the participants from the groups with developmental disorders differ in size and elongation from the group with TD suggesting a greater fixation instability. The visual noise affects all groups' gaze point patterns, implying more individual differences in the choice of the most informative parts of the image. The spread of the gaze distributions correlates negatively with the IQ scores, indicating that participants with lower intellectual abilities have more dispersed gaze positions.

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STRESS AND MENTAL DISORDERS IN THE COVID-19 PANDEMIC

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Nowadays, the fact that most people in Bulgaria underestimate the care for their mental health is being increasingly recognized. Unfortunately, for almost two years, humanity has been in a situation of a Covid-19 pandemic, which puts people's lives in an extreme situation, and mental health care must be a top priority, along with pandemic measures and health care.

This presentation will provide a brief overview of what stress is, the types of stress, and types of stress reactions. The typical mental disorders, mental experiences and consequences for people during the Covid-19 pandemic will be outlined in the context of disease-related stress and anti-pandemic restrictions. Special attention will be paid to three most common disorders (according to ICD 10) during the pandemic - Panic Disorder (PA), Generalized Anxiety Disorder (GAD) and Post-Traumatic Stress Disorder (PTSD). Different specific psychological phenomena (cognitive distortions) in post-Covid symptoms will be highlighted. The reported mental problems are extracted basing on observations of the work of Bulgarian psychotherapists and clinical psychologists, who conduct numerous online consultations.

Another goal of the presentation is to emphasize on the psychological consequences of not treating the described anxiety disorders. Basic measures will be outlined that can be taken

to reduce health damage by providing psychological assistance to victims of these disorders. It will be emphasized that anxiety disorders can be managed, but this depends on the acquisition of basic self-help and assistance skills. Finally, several typical cognitive distortions will be described that have been identified in people who appear in force majeure circumstances such as restrictions, negative news, bad messages from politicians, isolation, fear of getting sick with Covid 19, and uncertainty about the future.

DEVELOPMENT OF AUDITORY ATTENTION IN CHILDREN AND ADOLESCENTS: BEHAVIORAL STUDY

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BACKGROUND. "Attention is the taking possession of the mind, of one out of several simultaneously possible objects or trains of thought ... It implies withdrawal from some things in order to deal effectively with others" (James W., 1890). "The extent that selective attention skills are relevant for academic foundations and amenable to training, they represent an important focus for the field of education" (Stevens and Bavelier, 2012).

OBJECTIVE. The aim of the present work was to study the behavioral performance of children and adolescents during auditory selective attention task.

METHOD. In the auditory selective attention task, sequences of two stimuli with different frequency (40% targets and 60% non-targets) were presented randomly to the right and left ear. During the task participants maintained lateralized internal attention either to right- or left-side stimuli in order to produce selective motor responses with the right hand to targets appearing in the attended side. Thus, there were two conditions - attend-right and attend-left, each comprising 4 stimulus types - target-attended, non-target-attended, target-non-attended, non-target-non- attended. Correct response rate, reaction times (RTs) to targets, and response variance (RV) measured by RT standard deviation and coefficient of variance, were registered and analyzed in 110 normal, healthy, right-handed children and adolescents, divided into four age groups and two gender groups (9-16-years-old, age groups: 9-10, 11-12, 13-14 and 15-16-years-old). Effects of age, gender and side of attention were explored.

RESULTS. The rate of correct responses increased with age and was also significantly higher in the attend-right than attend-left condition. RTs decreased significantly with development and were significantly shorter in the attend-right than attend-left condition. RV decreased significantly with development. There were no significant differences in RV between attend-right and attend-left conditions. In addition, no performance or RT/RV gender differences were found between girls and boys.

CONCLUSIONS. These performance results demonstrate that the mechanisms of auditory selective attention progressively improve with development from 9 to 16 years. Notably, this developmental improvement is equally expressed in males and females. The observation that focusing internal attention to the right side produces faster and more accurate responses as compared to the attend-left responses may reflect effects of lateral asymmetry in sensory and

motor activations. Given that right-hand responses were required in the present task, the attend-right advantage implies a more efficient processing with unilateral activation of sensory and motor areas in only the left hemisphere, in contrast to the bi-lateral activation in the two hemispheres in the attend-left condition (right sensory and left motor areas). The proposed effects of (non)-lateralized activations persist as early as 9 years of age, do not change with development, and are independent of gender.

INFLUENCE OF SCHOOLBAG LOAD ON THE STATIC POSTURAL STABILITY OF 7-YEAR-OLD CHILDREN

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The schoolbags are the preferred choice due to the fact that they distribute the weight evenly on the spine without overloading only one shoulder. The schoolbag overload has negative effects on the correct posture and leads to neck, shoulder and back pain. In children this overload can lead to both temporary and chronic musculoskeletal problems. It was found that the weight of the load should not exceed 15% of the total body weight of the child carrying it. The aim of this study is to evaluate the effects of schoolbag load on the maintenance of static postural stability in 7-year-old children from elementary school.

The postural sway was measured by static posturographic system during quiet stance on firm support in six experimental conditions: stance with open eyes; stance with closed eyes without load and the same condition with backpack load with weights 2-3% and 16-17% of the child's body weight. Thirty-six participants took part in the investigation.

The results suggest that standing with a loaded backpack mostly affects the amplitudes of postural sway than its velocities. The stance with a backpack weighing about 16-17% of the body weight provoke the postural sways with higher amplitudes than stance without load in sagittal plane only. A significant increasement of amplitudes of postural sways in both conditions (stance with open and closed eyes) were observed.

This investigation show that the load on the back over 15% of the total body weight of the child increases the postural sway and leads to instability of static upright stance.

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Keyword: children, backpack weight, postural stability

AGE-DEPENDENT METABOLIC EFFECTS IN RATS WITH PINEALECTOMY

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The pineal gland is suggested to be an important area involved in programming of fertility, growth, aging and death of mammal via the released hormone melatonin. The aim of the present study was to ascertain the effect of melatonin deficit on several metabolic parameters, closely associated with aging process, at certain stages of ontogenesis. Sham and rats with pinealectomy, surgered at age of 3-, 14- and 18-months, respectively, were tested two months later. Age-related decline was demonstrated in sham-operated rats as decreased skeletal muscle strength, food intake as well as worsened calorimetric parameters. Pinealectomy decreased the maximal time to exhaustion, food intake, oxygen consumption, CO₂ production and energy expenditure during the dark period in the youngest rat group. In addition, melatonin deficit elevated blood pressure (systolic, diastolic and mean arterial pressure) as well as impaired serum glucose profile in 3-month-old rats with pinealectomy. In conclusion, the present study suggested that melatonin deficit accelerate aging associated with crucial physiological, metabolic and biochemical parameters in young adult rats.

Keywords: Pinealectomy, Aging, metabolism, Rats

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NEUROLOGICAL COMPLICATIONS AFTER COVID-19 INFECTION

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INTRODUCTION

COVID-19 pandemic has affected global health at an unprecedented rate, infecting 255 million people, while leading to death more than 5 million. The coronavirus subtype SARS-CoV-2, is an mRNA virus, which even though attacks primarily the cardiovascular and respiratory systems, it is a well-known fact that neurological manifestations are not being missed.

AIM

The aim of this literature review is to summarize the latest research data available and provide healthcare workers with an up-to date overview, regarding the neurological complications.

MAIN BODY

SARS-CoV-2 has a great affinity to the ACE2 receptor and it is supported that its migration, and subsequently, infection is facilitated by the transmembrane protease serine 2 (TMPRSS2) which helps with the viral binding to those receptors. ACE2 receptors are expressed primarily on the pulmonary alveolar cells, while extrapulmonary in the vascular endothelial cells of the GI tract, heart and brain and on the neurons and glial cells. Therefore, apart from respiratory (dry cough, dyspnea) and cardiovascular symptoms (blood clots, ischemia), neurological features are also manifested e.g. anosmia, ageusia, myalgias. More specifically, encephalitis, meningoencephalitis and seizures, are common complications which follow COVID-19 infection. Intracerebral hemorrhage and hemophagocytic lymphohistiocytosis are conditions, that even though have different pathophysiological mechanisms, both are life threatening. Regarding demyelinating disorders, Guillain Barré syndrome may be presented even after primary infection while transverse myelitis and acute disseminated encephalomyelitis are not often presented clinical entities. Multiple Sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD), which are classified as neurodegenerative diseases, are suggested to be linked both as risk factors and long term complications due to neuronal damage and loss.

CONCLUSION

In view of the above, COVID-19 can affect the human organism unpredictably, having complications ranging from mild to severe. However, there is not enough information on whether or not SARS-Cov-2 infection could accelerate AD, PD, and MS presentation in the long term and more research needs to be done.

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IN VITRO EVALUATION OF THE EFFECTS OF NEWLY SYNTHETIZED HYDRAZONES AND 1,3,4-OXADIAZOLES DERIVATIVES ON ISOLATED RAT BRAIN SYNAPTOSOMES AND HUMAN RECOMBINANT MAO-B ENZYME

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This study evaluates the *in vitro* effects of two series compounds: 1,3,4-oxadiazoles (**3a-k**) and hydrazones derivatives (**5a-n**) on isolated rat brain synaptosomes and human recombinant MAO-B enzyme (hMAO-B). In order to evaluate drug likeness of these newly synthesized molecules, *in-silico* ADME evaluation was carried out.

On isolated rat brain synaptosomes, administered alone at concentration 40 μ M, both series revealed weak statistically significant neurotoxic effects, compared to the control (non-treated synaptosomes). In conditions of 6-hydroxydopamine-induced oxidative stress, all the compounds showed statistically significant neuroprotective effects, by preserving the synaptosomal viability and the level of reduced glutathione, compared to the toxic agent.

On the activity of human recombinant MAO-B enzyme (hMAO-B), all derivatives didn't show statistically significant inhibitory effect, compared to the control (pure hMAO-B).

Of the series of substances studied, only **3a** and **3d** showed a statistically significant inhibitory effect on the activity of human recombinant MAO enzyme (hMAOB). The inhibitory activity of the substances is close to that of Selegiline.

2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole **3a** inhibits enzyme activity by 44%, 3-(5-phenyl-1,3,4-oxadiazol-2-yl)-1H-indole **3d** inhibits by 46%, and Selegiline (classic MAOB inhibitor) - reduces enzyme activity by 55% compared to the control (pure hMAOB). It is worth mentioning that 2,5-substituted 1,3,4-oxadiazoles would represent a productive matrix for the development of new class of MAOB inhibitors.

ANALGESIC EFFECTS OF VALORPHIN PEPTIDE ANALOGS WITH UNNATURAL CYCLIC AMINO ACIDS IN RATS

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Introduction. VV-hemorphin-5 (Valorphin or V1) is an endogenous peptide that shows a significant antinociceptive effect. The subject of the present study is two newly synthesized valorphin peptides (C5-V and C6-V) with unnatural cyclic amino acids. Our previous experimental data indicate that intracerebroventricular injection of VV-hemorphin-5 and its analogs causes dose-dependent antinociceptive effects in a formalin test. The aim of the present study was to evaluate the effects of intraplantar injected V1, C5-V, and C6-V on the Carrageenan-induced hyperalgesia as compared to the reference anti-inflammatory and analgesic drug Indomethacin.

Methods. The Fmoc chemistry (solid-phase peptide synthesis) was used to synthesize two new analogues of Valorphin – C5-V (Val-Val-Tyr-**AC5C**-Trp-Thr-Gln-NH₂) and C6-V (Val-Val-Tyr-**AC6C**-Trp-Thr-Gln-NH₂). Based on previous data, all peptides were injected intraplantar in the right hind paw at a dose of 50 µg / 5 µl per rat, 5 minutes before the irritant. The inflammatory process was caused by injecting 100 µl of carrageenan 1% into the same hind paw. The nociceptive effect was assessed using a paw pressure analgesimeter at 1, 3, and 4 hours after carrageenan injection.

Results. Experimental data show that carrageenan-induced inflammation lowers the mechanical pain threshold in the injected paw. V1 showed a significant analgesic effect in the ipsilateral paw at 1st, 3rd, and 4th hours after carrageenan injection. Its effect was higher compared to the reference Indomethacin. C5-V showed a significant antinociceptive effect, comparable to that of V1 after the 1st hour. C6-V also showed a considerable analgesic effect, and its effect was comparable to those of Indomethacin but lower to the V1 induced antinociception.

Conclusion. The results demonstrated a significant and long-lasting local antinociceptive effect of Valorphin in the paw pressure test, while its synthetic analogs C5-V and C6-V showed a lower but comparable to the reference antinociceptive effect of Indomethacin.

Keywords: valorphin peptides, nociception, rats

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MELATONIN PROTECTIVE EFFECT AGAINST A β - INDUCED NEUROTOXICITY AND MEMORY IMPAIRMENT IN ICV A β ₁₋₄₂ RAT MODEL WITH PINEALECTOMY

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Melatonin is a multifunctional molecule and its role in the regulation and protection of the central nervous system is well documented. Therefore, melatonin was proposed as a possible therapeutic agent for reducing the severity of Alzheimer's disease (AD), a progressive neurodegenerative disease characterized by cognitive decline and memory dysfunction. In addition, melatonin has a higher preference in comparison to other available antioxidants in the therapeutic strategy of AD due to its inhibitory effect on amyloid beta (A β ₁₋₄₂) accumulations, low toxicity effect in high doses, and readily passage through blood brain barrier. Pinealectomy appears to be a good model to study melatonin deficiency and pathway dysfunction in the pathogenesis of neurodegenerative diseases.

Hence, we investigated the effect of melatonin on a reduction of the neurotoxicity expressed by A β and γ -secretase production and memory loss in icv A β ₁₋₄₂ rat model of AD combined with melatonin deficiency. Animals (ten weeks old male Sprague-Dawley rats) undergone icv infusion of A β ₁₋₄₂/vehicle, were injected with melatonin (50 mg/kg, intraperitoneally (i.p.)/vehicle about two hours before the onset of the dark phase for 40 days. Object recognition test (ORT) and radial arm maze test (RAM) were used to explore cognitive functions. Amyloid beta and gamma secretase levels were measured in the frontal cortex (FC) and the hippocampus. Pinealectomy did not exacerbate associative and spatial memory of A β ₁₋₄₂-treated rats in ORT and RAM, respectively. Chronic melatonin administration corrected impaired cognitive performance in both AD model and AD model combined with melatonin deficit. The A β ₁₋₄₂ secretion was significantly increased compared to sham group in the FC and the hippocampus in the A β ₁₋₄₂ rats with pinealectomy which effect was compensated by melatonin treatment. The main enzyme which is responsible for A β accumulation – γ -secretase, was elevated in the A β -pin groups and the treatment with melatonin lowers the levels to the control values. The present data suggest pinealectomy+A β ₁₋₄₂ rat model as a more reliable model of AD. Melatonin could have a substantial potential to suppress A β ₁₋₄₂ accumulation in the brain and concomitant memory impairment

Keywords: icvA β ₁₋₄₂; melatonin; A β , γ -secretase, memory loss; rat

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EFFECT OF PREDNISOLONE AND IMATINIB MESYLATE ON AMIODARONE-INDUCED PULMONARY FIBROSIS IN RATS

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The experimental model of amiodarone (AM)-induced lung toxicity is one of the relevant models to study pulmonary fibrosis. AM administered intratracheally induces inflammatory response, activation of fibroblasts, and subsequent fibrosis. We tested the anti-inflammatory and antifibrotic effect of imatinib mesylate (IM) and prednisolone (PR) against AM-induced pulmonary fibrosis in a rat model.

Methods: The study was carried out on 72 male Wistar rats divided into six treatment groups: control; AM group – treated intratracheally with AM on days 0 and 2; PR1 group – treated with AM and PR 10 mg/kg orally from day 0 to day 10; PR2 group – treated with AM and PR from day 10 to day 28; IM1 group – treated with AM and IM 50 mg/kg orally from day 0 to day 10; IM2 group – treated with AM and IM from day 10 to day 28. Pulmonary fibrosis was assessed by measuring hydroxyproline (HP) and collagen (COL) content in lung homogenate (LH) and histopathologically on day 28 after AM administration.

Results: AM resulted in significantly increased HP and COL content in LH on day 28. The content of HP and COL in LH of animals, treated with AM and PR, given after day 1 and AM plus IM, given after day 10 were decreased compared to AM alone on day 28 ($p < 0.05$).

Intratracheal AM led to moderate interstitial and perivascular fibrosis, thickening of interstitial spaces and cellular infiltration; these damages were attenuated by above-mentioned dosing regimens.

Conclusion: The results obtained from our study showed that pulmonary fibrosis was attenuated by IM, given during fibrotic phase and by PR, given during inflammatory phase.

Keywords: amiodarone, imatinib mesylate, lung fibrosis, prednisolone

AGOMELATINE ATTENUATES BEHAVIORAL CHANGES IN TWO RAT MODELS OF SPORADIC ALZHEIMER'S DISEASE

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In two consequential studies we have investigated the effect of agomelatine against behavioral, biochemical and histological impairments in streptozotocin (STZ) and amyloid beta (A β) induced model of ADs in male rats. The agomelatine, which is a melatonin MT1 and MT2 agonist and 5-HT_{2C} antagonist, was injected intraperitoneally for 30 days, at a dose of 40mg/kg in both studies. We measured the anxiety levels, spatial memory errors and anhedonia by using the following methods: Elevated Plus Maze (EPM), Radial Arm Maze (RAM), Saccharine Preference Test (SPT). The treatment with A β significantly decreases the

number of entries in to the aversive open arms of the EPM and the time spent inside of them for the A β group. Reduced anxiety-like behaviour, tested with the EPM, was observed and in the study with STZ-treated rats as they spent longer time on the open arms and made more entries, compared to the group with sporadic AD. Agomelatine corrected anxiety behavior of A β rats as the treated animals enter the open arms more often and spend significantly longer time in there. Administration of agomelatine decreased working memory errors during the last two sessions in RAM in the model with izvSTZ-induced AD. Testing the A β -induced animals showed alleviation in the spatial memory impairment only during the last session. The SPT helped us to investigate the level of anhedonia as a marker of depressive-like behaviour, which is considered as a comorbid condition in AD. Preference for sweet solutions has decreased after icv infusion of A β and STZ. The A β -veh and STZ-veh groups demonstrated anhedonia, compared to the sham-veh group. Agomelatine reversed depressive-like response induced by icv infusion of both toxins, compared to the control groups and increased the preference to saccharine. The ability of Ago to alleviate behavioral symptoms observed in the two models of sporadic ADs suggests that this melatonin alternative can be considered a promising adjuvant in this disease.

PIROMELATINE TREATMENT RESTORES IMPAIRED SLEEP-WAKE CYCLE AND SLEEP ARCHITECTURE THROUGH MELATONIN RECEPTORS IN MALE AND FEMALE OFFSPRING RATS WITH PRENATAL STRESS

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The prenatal stress (PNS) model in rodents is known to impair circadian rhythms of sleep/wake cycles. Piromelatine (Pir) is a novel melatonin analog designed for the treatment of insomnia. The present study was aimed to explore the effects of Pir and the role of melatonin receptors on PNS-induced impaired sleep architecture and rhythmicity of sleep/wake cycle and in a rat model of PNS in male and female offspring. The electroencephalographic (EEG) and electromyographic (EMG) recording for up to 24 h were analyzed under basal conditions (12:12 LD cycle+vehicle), PNS+vehicle, PNS+Pir (20 mg/kg/day for 7 days) and PNS+Pir+Luzinodol (Luz) (10 mg/kg) conditions. The rats exposed to PNS were characterized by disturbed sleep/wake cycle associated with diminished NREM sleep, elevated REM sleep and wake pattern in a sex-dependent manner. Piromelatine corrected impaired sleep architecture and sleep-wake cycle, while the melatonin (MT) receptor antagonist Luz suppressed the beneficial effect of this melatonin analog. Our findings suggest that Pir can exert sex-dependent beneficial effects on PNS-induced impaired sleep architecture and rhythmicity of sleep/wake cycle via MT receptors.

Keywords: prenatal stress, Piromelatine, sleep/wake cycle, sleep architecture, MT receptors

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DECREASED EXPRESSION OF BDNF IN THE HIPPOCAMPUS AFTER PRENATAL STRESS IN RATS IS ASSOCIATED WITH CHANGES IN SPATIAL MEMORY IN A SEX-DEPENDENT MANNER: EFFECT OF PIROMELATINE

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Prenatal stress (PNS) leads to cognitive alterations mainly observed later in life. We investigated the effects of piromelatine, a mixed (MT1) and MT2 and serotonin (5-HT) 1A/1D receptors agonist and 5-HT2B receptor antagonist, on hippocampus-dependent spatial memory and concomitant changes in BDNF levels in male and female rat offspring with a history of prenatal stress. Different stressors were applied on pregnant female rats, which started on the 7th gestational day and continued until birth. At the age of 60-days, offsprings were injected every day with piromelatine/vehicle at a dose of 20 mg/kg for 21 days. Hippocampus-dependent spatial memory was explored in the radial arm maze test (RAM). The BDNF level in the hippocampus was measured by ELISA. A deficit in spatial memory was detected in male but not female rats with prenatal stress compared to their matched controls. Chronic piromelatine treatment corrected the altered memory function and decreased both working and double memory errors in the last trial of the RAM task in the male PNS offspring. The prenatal stress decreased the expression of BDNF in the hippocampus of male offspring with prenatal stress while female offspring were not affected. The melatonin analogue elevated BDNF in male offspring. The present findings suggest that the novel drug piromelatine could positively affect spatial memory via BDNF in the hippocampus in a sex-dependent manner in rats with a history of prenatal stress.

Keywords: prenatal stress, Piromelatine, memory deficit, BDNF

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THE ROLE OF AGE AND MELATONIN DEFICIENCY ON EMOTIONAL STATUS AND LEVEL OF OXIDATIVE STRESS IN EXPERIMENTAL RATS

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The pineal gland has a crucial role on development and aging process via the released hormone melatonin. In the present study, we aimed to evaluate the influence of melatonin deficit at different aging stages on behavior and oxidative stress level in the hippocampus of rats operated 3-, 14- and 18-month-old. The anxiety and depressive-like behavior was elevated in age-depended manner in the sham-operated rats. The removal of the pineal gland induced increased locomotor activity in the open field of the youngest group and provoked depressive-like behavior in both rats operated 3- and 14-month-old, respectively. The superoxide dismutase (SOD) activity was enhanced in the sham-operated 14-month-old rats compared to the matched younger rats while there were no changes in the level of glutathione (GSH) among different ages in the sham groups. The lipid peroxidation was elevated in mature and aged rats compared to the youngest sham rats. Pinealectomy suppressed the activity of SOD and GSH and increased malondialdehyde level in the hippocampus compared the matched sham 14-month-old rats. In conclusion, our results suggest that behavioral responses associated with emotional status and oxidative stress level are vulnerable to changes in young and mature rats with pinealectomy while melatonin deficiency has no impact in elder animals.

Keywords: Age, Melatonin, behavior, oxidative stress, rat.

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EFFECT OF OBESTATIN ON MAXIMAL FORCE OF CONTRACTION OF EXCISED FROG HEART AFTER CHEMICAL SYMPATHECTOMY WITH 3-IODOTHYROSINE

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The aim of this study is to investigate the positive inotropic effect of obestatin in the presence of 3-iodothyrosine (3-IT) in heart preparations of *Pelophylax ridibundus* frog. It is known that, the myocardial β -adrenoreceptors and protein kinase A downstream targets are responsible for the observed positive inotropic effect of obestatin. The application of obestatin

(1 nmol/l and 100 nmol/l) significantly enhances the force of contraction of excised and cannulated frog hearts. This effect was completely blocked in the presence of 3-IT, a selective inhibitor of tyrosine hydroxylase that is the rate-limiting enzyme in the catecholamine biosynthesis chain. 3-IT was injected into the dorsal lymph sac 1 hour before isolation and cannulation of the heart at a dose of 0.02 mg/g b.w. It is concluded that, the treatment with 3-IT inhibits adrenaline synthesis and in this way abolishes adrenaline mediated positive inotropic effect of obestatin.

Keywords: Obestatin, Cardiac, Hormone, Autonomic nervous system, In vitro, Sympathectomy

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