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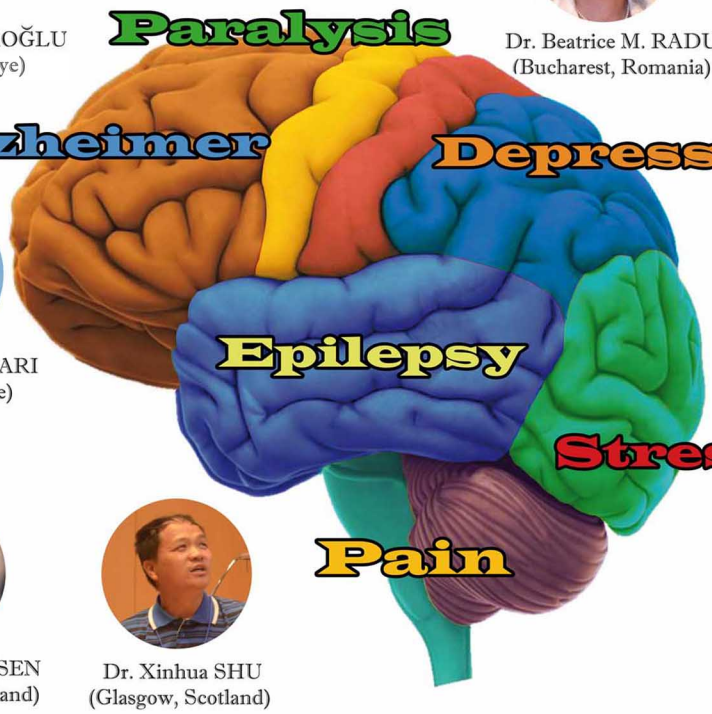
Dr. Mustafa NAZIROĞLU
(Isparta, Türkiye)

Dr. Beatrice M. RADU
(Bucharest, Romania)

Dr. Denis ROUSSEAU
(Grenoble, France)



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(Grenoble, France)

Dr. Nashat ABUMARIA
(Shanghai, China)

Dr. Simon HEBEISEN
(Biningen, Switzerland)

Dr. Xinhua SHU
(Glasgow, Scotland)

Dr. Ferah YILDIRIM
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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A- Ion Channels (Na^+- K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-Clamp applications)

B- Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D- Gene and Oxidative Stress
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

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Biophysics	Biochemistry
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Keywords
Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

7th International Brain Research School

Abstract Book

of

7th International Brain Research School

27 June - 03 July 2022

Isparta, Türkiye

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SPEAKERS

Speak No. 1

Fluorescent Ca^{2+} stains for imaging the mice microglia

Mustafa NAZIROĞLU[1,2]

[1]Neuroscience Research Center (NÖROBAM), Suleyman Demirel University, Isparta, Türkiye

[2]Drug Discovery Unit, BSN Health, Analyses, Innovation, Consultancy, Organization, Agriculture, Industry LTD, Isparta, Türkiye

Microglia are the resident immune cells of the central nervous system. It is well-known that accumulation of Ca^{2+} in the activated microglia is the main cause of several pathologies such as apoptosis and excessive reactive oxygen species production in the several disease models.

Calcium ion concentration is ten thousand times higher outside of neurons as compared to the inside of neurons. The Ca^{2+} passes the cell membrane via the activation of cation channels such as voltage gated calcium and chemical gated calcium channels. In addition to the cation channels, TRP superfamily with 28 members was discovered within the last decades. As a member of the TRP superfamily, TRP melastatin 2 (TRPM2) is stimulated in several cells by ADP-ribose and oxidative stress (Perraud et al 2001; Nazıroğlu and Lückhoff 2008). For investigation of the activation of TRPM2, the calcium imaging by using the laser scan confocal microscope is a most valuable technique. In our experiments, we have been used the Fluo-3-AM and Fluo-8 dyes for the investigation of TRPM2-dependent Ca^{2+} influx in several neurons, including microglia (Yıldızhan and Nazıroğlu 2020). The green images of the neurons were captured in the laser scan confocal microscope after the staining of the neurons with Fluo-3. A ratiometric analysis of Ca^{2+} concentration in the neuron is Fura-2/AM. The analysis was also used in our experiments.

In conclusion, it seems that the laser scan confocal microscope is a most valuable imaging technique for the investigation of TRPM2 channel.

Keywords: Fluo-3; Laser scan confocal microscope; TRPM2 channels: Microglia

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SPEAKERS

Speak No. 2

Low-energy accelerated protons irradiation inhibits DNA repair and diminishes cell proliferation, migration and calcium signaling in brain microvascular endothelial cells

Roberta STOICA[1,2], Călin Mircea RUSU[1], Mihai RADU[2], Beatrice Mihaela RADU[1]

[1]Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucharest, 050095, Romania

[2]Department of Life and Environmental Physics, 'Horia Hulubei' National Institute for Physics and Nuclear Engineering, Măgurele, 077125, Romania

Modern radiotherapeutic approaches are focused on the delivery of a precise high dose of radiation within the tumor volume whilst minimizing damage to surrounding normal tissue. In this context, accelerated proton beams are described to deposit their energy in a finite fixed Bragg peak at depth in tissue with no dose / minimal dose beyond this point. Beside the direct action of low-energy accelerated protons against tumoral cells, few studies have focused on the effects on non-tumoral cells, i.e. lymphocytes (George et al. 2015). On the hand, considering that tumors are intensely vascularized, only few studies have discussed their effects on brain vasculature. The aim of our study is to analyze the functional activity changes induced by low-energy accelerated protons in brain microvascular endothelial cells.

To this purpose, we irradiated bEnd.3 endothelial cells (ATCC) to low-energy accelerated protons (energy below 10 MeV) in the cyclotron TR19, in the dose range 0-10 Gy, dose rate 1Gy/min. The characterization of the proton beam was done by dosimetry measurements and Monte-Carlo computational modeling in Geant4 software. After irradiation, we evaluated the cellular proliferation and migration by the clonogenic test, the wound healing test and the MTT assay. We also analyzed the DNA repair by the micronuclei test and the gama-H2Ax method. The functional changes induced by irradiation were also explored by Fura-2 calcium imaging recordings.

We demonstrated that by increasing the radiation dose and the linear energy transfer (LET) we obtain a significant inhibition of the DNA repair capacity. At high dose and high LET, we evidenced a reduction of the cellular proliferation and migration. We also analyzed the alteration induced by irradiation on several parameters of the calcium transients activated by ATP in brain microvascular endothelial cells.

Considering the extended use of bEnd.3 endothelial cells in the pharmaceutical industry, our data are valuable and the *in vitro* model of the blood brain barrier exposed to radiation could be further employed for extended drug testing with high relevance in oncology.

Keywords: Blood brain barrier; Low-energy accelerated protons; Hadrontherapy; Oxidative stress

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SPEAKERS

Speak No. 3

Behavioral assays and animal models of psychiatric disorders

Nashat ABUMARIA
State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Institutes of Brain Science, Fudan University, Shanghai 200032, China. **E-mail**: Abumaria@fudan.edu.cn

Animal models are important tools in the study of human diseases and/or disorders. They allow us to use research methods (cannot be used in humans) to understand underlying pathological mechanisms and screen for/identify/test new therapeutic agents. Consequently, scientists have developed several criteria to assess the validity and reliability of the behavioral assays and/or animal models of human disorders. Regarding psychiatric disorders (e.g. anxiety, depression and schizophrenia) many of the symptoms used to diagnose these disorders in humans (e.g., hallucinations, delusion, anxiety, intrusion of traumatic memories, sadness, guilt) are hard to be convincingly established in animals. Furthermore, unlike other brain diseases (e.g. Alzheimer's, Parkinson's, ALS and stroke), the exact pathological mechanisms underlying psychiatric disorders are unknown making it even harder to establish a convincing animal model. We will discuss the importance of animal models in neuroscience. An overview of classical literatures summarizing definitions of animal models, criteria to establish their validity and additional assessments to establish their reliability will be presented. We will zoom in and focus on behavioral assays and animal models relevant to psychiatric disorders. Students will be introduced to animal models of fear memory, depression, helplessness and schizophrenia as well as to some behavioral assays that are used to establish relevant behaviors. Behavioral assays and animal models of psychiatric disorders do demonstrate reasonable correlates to human symptoms (e.g. motivational, exploration, reward and cognitive deficits). Thus, they are indispensable tools to study mechanisms underlying psychiatric disorders and identify new treatments. Extra efforts are required, however, to exclude confounding factors and/or alternative interpretations of the behavioral readouts.

Keywords: Animal models; Psychiatric disorders; Fear memory; Anxiety; Depression; Schizophrenia

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SPEAKERS

Speak No. 4

Mapping genome-wide DNA methylation changes in alcohol use disorder

Ferah YILDIRIM
Charité - Universitätsmedizin Berlin, Department of Neuropsychiatry, Berlin, Germany

No Abstract

SPEAKERS

Speak No. 5

Principles of Ca^{2+} imaging using low-affinity indicators

Marco CANEPARI
Univ. Grenoble Alpes, CNRS, LIPhy, F-38000 Grenoble, France

Ca^{2+} is the most universal molecular messenger in biology providing two types of signals when it enters the intracellular cytoplasm. It specifically binds to proteins physically interacting with the Ca^{2+} channel in nanoscale domains and it increases the cytosolic Ca^{2+} concentration binding to proteins in unspecific manner. The experimental measurement of Ca^{2+}, however, consists in introducing a Ca^{2+} sensitive fluorescent buffer that alters the physiological Ca^{2+} signalling.

In this lecture I will introduce the principles of Ca^{2+} imaging using low-affinity indicators and its applications to investigate the truly physiological Ca^{2+} dynamics in native systems.

I will first analyse in detail the issue of competition of the Ca^{2+} indicator with the endogenous Ca^{2+} buffers expressed by the cell and how Ca^{2+} imaging can be performed to monitor the free Ca^{2+} concentration without perturbing the physiological Ca^{2+} homeostasis.

Second, I will show how the fast equilibration of low-affinity indicators can disclose the physiological kinetics of voltage-gated Ca^{2+} channels underlying neuronal excitability.

Third, by combining Ca^{2+} imaging with membrane potential imaging, I will show how low-affinity indicators can unravel the occurrence protein activation at nanoscale domains.

I will finally illustrate how neuronal computation can be exploited to analyse data and extract the ensemble of ionic currents.

Keywords: Calcium, ion channels, neuronal excitability

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SPEAKERS

Speak No. 6

Western blot analyses in the mitochondria

Denis ROUSSEAU
LMGP – IMBM, UMR 5628, Institut National Polytechnique PHELMA 3, parvis Louis Néel, BP257, Grenoble Alpes University, Grenoble Cedex 1, France.

Mitochondria have several central actions in the cell metabolism, and its most important action is cellular ATP synthesis, but importantly also as crucial players in lipid metabolism. Indeed, mitochondria have pivotal role in the carbohydrate and lipid metabolism, and they have also lipid storage function. Mitochondria are involved in lipolytic processes through the β-oxidation of lipids. The processes of lipogenesis require mitochondrial biogenesis, which itself requires, among many others, the correct expression of the mitochondrial inner membrane protein ATAD3 (ATPase family AAA domain-containing protein 3). ATAD3 has an essential role on the ATPase in mitochondrial biosynthesis (Li et al. 2016). Western blot analysis is an essential technique for the investigation of protein bands. It is also valuable technique for the investigation of ATAD3 (Li et al. 2014).

In the presentation, I will summarize the technique in the analyses of ATAD3. In addition, I will give more details on the clues of the Western blot analyses in the mitochondria.

Keywords: ATAD3; Mitochondria; Western blot

References

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SPEAKERS

Speak No. 7

Protection of p-Coumaric acid against depression and memory impairment via inhibition of neuroinflammation

Xinhua SHU[1,2]
[1]Department of Biological and Biomedical Sciences, Glasgow Caledonian University, Glasgow, UK
[2]School of Basic Medical Sciences, Shaoyang University, Shaoyang, P.R. China

Depression, a common mental disorder, affect over 5% of adults and causes disability worldwide. The clinical symptoms include weight change, sadness, despair, anhedonia, social withdraw and memory impairment. Approximately 30% patients are partially or entirely unresponsive to current antidepressants. It is urgently needed to develop new medication for depression. P-Coumaric acid (p-CA), a natural phenolic acid, has been shown the capacity against inflammation, which contributes to the development and progression of depression. We treated the depressive mice with p-CA and found p-CA treatment alleviated depression-like behaviour and improved memory. We used network pharmacology to investigate the underlying mechanism and found p-CA had multiple targets and mediated a wide range of signalling pathways, of which inflammation-associated targets and signalling are predominant. We confirmed the BDNF-AGE-RAGE-NF-kB axis was associated the protection of p-CA in depression.

Our data sheds light on the functional mechanisms of p-CA and suggests p-CA has therapeutic potential for patients with depression. In this talk, I will update the recent progress in research of depression and present our findings from depressive mouse models.

Keywords:
P-Coumaric acid; Depression; Neuroinflammation.

SPEAKERS

Speak No. 8

State dependent block of voltage gated sodium and calcium channels as modern treatment for epilepsy

Simon HEBEISEN
B'SYS GmbH, The Ionchannel Company, Witterswil, Switzerland

Epilepsy is the fourth most common neurological disorder and affects people of all ages. Medication for epilepsy is often life-long and has a major impact on the quality of life - mostly being related to substantial adverse effects. Therefore, over 30% of people with epilepsy do not achieve sufficient seizure control whilst effective medication being available.

Ion channels are often primary targets of anticonvulsant drugs. They can either act as blockers for voltage gated sodium and calcium channels or as activators for potassium or chloride channels. Additionally, modulators of ligand gated ion channels ($GABA_A$ or Glutamate receptors) are frequently used to treat epilepsy.

Employing a panel of functional electrophysiological assays using patch-clamping on a broad range of voltage and ligand gated ion channels, we were able to successfully screen for drugs with a beneficial action profile. In successful leads we found drugs that selectively interacted with TTX sensitive, neuronal voltage gated sodium channels. Activation and fast inactivation were unchanged, while an increased affinity in the slow inactivated state was observed. This is a modern mode of action for anticonvulsive drugs. In contrast, traditional anticonvulsant drugs often show their major effects on the fast inactivated state of voltage gated sodium channels.

For further improvement, new anticonvulsants interacting with multiple ion channels as primary targets should be developed. As promising targets one isoform of the TTX sensitive voltage gated sodium channels and a voltage gated calcium channel were identified. For the screening of larger number of compounds, automated patch-clamping was used. Before starting the screening of compound libraries, stably transfected cell lines with constant expression levels were developed and biophysically characterized.

Based on the results of these experiments an assay was developed to be able to reliably differentiate effects on ion channels in certain states and at high throughput.

Keywords: Epilepsy, voltage gated sodium channels, voltage gated calcium channels, state dependent inactivation, patch-clamp technique.

Oral Presentations

Oral Presentation 1

Diabetic neuropathic pain and TRPM2 Channel: Focus on selenium

Bünyamin AYDIN
Division of Endocrinology and Metabolism, Department of Internal Medicine, Kutahya Evliya Çelebi Training and Research Hospital, Faculty of Medicine, University of Health Sciences, TR-64100, Kutahya, Türkiye

Diabetes mellitus (DM) induces several chronic complications, including the diabetic neuropathy (DiNP). Increased reactive oxygen species (ROS) and decreased antioxidant levels have been implicated in the pathogenesis of DiNP. The increase of intracellular free Ca^{2+} ($[Ca^{2+}]_i$) concentration is an important factor leading to the ROS enhancement in the hyperglycemia. Dorsal root ganglion (DRG) neurons as the primary sensory neurons were mainly affected by DiNP. A calcium permeable TRP channel is TRPM2., and it is activated by DNA damage-induced ADP-ribose and oxidative stress. Accumulating data indicated that the increased activation of TRPM2 is responsible via the increase of $[Ca^{2+}]_i$ concentration, ROS, and apoptosis levels for the increase of DiNP (Kahya et al. 2017). The expression levels of TRPM2 in the DRG neurons are high (Vandewauw et al. 2013).

The results of recent studies indicated that selenium as an effective anti-diabetic agents exerted several positive effects, including antioxidant, anti-apoptotic (Steinbrenner et al. 2022), and TRP channel modulator (Kahya et al. 2007) actions in DRG neurons. In the oral presentation, I will review the modulator action of selenium on the Ca^{2+} influx-mediated neuropathy, oxidative neurotoxicity, and apoptosis via the modulation of TRPM2 in DRG of rodents with DM.

The present literature results indicate that DM-mediated TRPM2 activation has a main role in the DM-induced neuropathic pain, oxidative DRG neuron injury and apoptosis in the experimental animals, although they were modulated by the treatment of selenium.

Key words: Antioxidants; Diabetic neuropathic pain; DRG injury; Oxidative stress; TRPM2 channel.

References

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Oral Presentations

Oral Presentation 2

Agomelatine attenuates calcium signaling and apoptosis via the inhibition of TRPV1 channel in the hippocampal neurons of rats with chronic mild stress depression model

Gülin Özdamar ÜNAL [1], Arif DEMIRDAŞ [2], Mustafa NAZIROĞLU [2,3], İshak Suat ÖVEY[4]

[1]Department of Psychiatry, Faculty of Medicine, Suleyman Demirel University, Isparta, Türkiye.
[2]Neuroscience Research Center, Suleyman Demirel University, Isparta, Türkiye.
[3]Drug Discovery Unit, BSN Health, Analysis and Innovation Ltd. Inc. Teknokent, Isparta, Türkiye.
[4]Department of Physiology, School of Medicine, Alanya Alaaddin Keykubat University, Alanya, Türkiye.

Background

According to the data from the World Health Organization, major depression is reported as a prevalent disease worldwide, and it affects approximately 264 million individuals (WHO 2020). Due to its long-lasting attacks, high chronicity, exacerbation, and recurrence rates, major depression is seen as the main cause of disability (Kessler et al. 2005; GBD 2017). The unique disorder that leads to depression is still uncertain and is likely to show individual differences. Studies on the biological etiology of depression emphasize the interactions among hormonal changes that arise as a response to stress, biochemical, environmental, genetic, and epigenetic factors (Dean and Keshavan 2017). The fact that effectiveness in the treatment of depression is not at the desired level, problems regarding side effects and reliability, and treatment compliance problems mostly caused by these have led researchers to conduct studies for shedding light on its etiopathogenesis and develop new medications.

Disruption of the balance inside the cell between reactive oxygen species (ROS) and antioxidants is defined as oxidative stress (Rahal et al. 2014). Oxidative stress triggers programmed cell death (apoptosis) by causing damage to structures in the cell such as proteins, lipids, and deoxyribonucleic acid (DNA) (Czarny et al. 2020). In recent studies, it has been shown that the oxidative balance is disrupted in many psychiatric diseases, especially depression, schizophrenia, bipolar disorder, anxiety disorder, attention deficit and hyperactivity disorder, autism, and Alzheimer's (Salim 2014). An important area of research in the field of mental disorders is the mechanisms by which abnormalities in oxidative metabolism cause diseases.

One of the important mechanisms in the etiopathogenesis of depression is cytosolic Ca^{+2} flow. It has been shown that transient receptor potential vanilloid 1 (TRPV1) channels are vulnerable to oxidative stress and cation channels are mainly permeable to Ca^{+2}. TRPV1 channels are implicated in modulating synaptic transmission, neurogenesis, and microglial neuron communication (Storozhuk et al. 2019).

Agomelatine activates the suprachiasmatic MT1 and MT2 receptors by binding to them. Agomelatine is a moderate 5-HT2C receptor antagonist in the central nervous system, although it does not interact with other serotonin receptor subtypes (Guardiola-Lemaitre et al. 2014). There is no study in the literature that investigated TRPV1 channel-mediated cytosolic Ca^{+2} ion entry and the regulating effects of agomelatine on TRPV1 channels in hippocampal cells in a depression model induced by Chronic Mild Stress (CMS). The purpose of this study is to explore the regulatory function of agomelatine on TRPV1 channels in cytosolic calcium ion increase, as well as its effects on intracellular calcium levels and hippocampal apoptosis.

Methods

To investigate the TRPV1 channel-mediated effect of agomelatine, the CMS model, which is a well-validated model in rats, was utilized. The rats were divided into six main groups: Control, Dimethyl sulfoxide (DMSO), AGOM, CMS, CMS+DMSO, and CMS+AGOM. Five weeks of chronic mild stress were applied to the CMS groups. The validity of the CMS model was confirmed with the sucrose preference test

(SPT). Drug treatments were applied in the last 3 weeks of the experiment. On the hippocampus tissue, cell Ca^{+2} signal, apoptosis, caspase 3 and 9 enzyme activity, lipid peroxidation (LPO), and cell viability analyses were conducted.

Results

The baseline sucrose preference index (SPI) did not differ significantly across groups. Evaluation of the sucrose preference test conducted on the 21st day of the experiment revealed a statistically significant difference between the groups ($p < 0.001$). The post-hoc analysis demonstrated a statistically significant difference in SPI between the control group and the CMS, CMS+DMSO, and CMS+AGOM groups ($p < 0.001$ for all three groups). On day 42, a statistically significant difference was observed between the study groups in the sucrose preference test ($p < 0.001$), and it was determined that the statistically significant difference was due to comparisons between the control group and the CMS ($p<0.001$) and CMS+DMSO ($p < 0.001$) groups.

Compared to the control group, the $[Ca^{2+}]_i$ concentrations were significantly increased in the CMS ($p < 0.001$), CMS+DMSO ($p < 0.001$), and CMS+AGOM ($p < 0.05$) groups. AGOM lowered them in the CMS+AGOM groups. In addition, CPZ treatments reduced them even more in the CMS+CPZ and CMS+AGOM+CPZ groups ($p < 0.05$). There was no significant difference between the control, DMSO, and AGOM groups.

The levels of apoptosis ($p < 0.001$), caspase -3 ($p < 0.05$), and caspase -9 ($p < 0.05$) were higher in the CMS and CMS+DMSO groups compared to the control, DMSO, and AGOM groups. However, their levels reduced after treatment with AGOM. Apoptosis ($p < 0.001$), caspase -3 ($p < 0.05$), and caspase -9 levels ($p < 0.05$) were lower in the CMS+AGOM and AGOM groups than in the CMS and CMS+DMSO groups. CMS exposure decreased the levels of cell viability in the CMS and CMS+DMSO ($p<0.05$). Nevertheless, they were not elevated by AGOM therapy.

Indicative of oxidative stress, the levels of LPO were significantly ($p < 0.001$) higher in the CMS and CMS+DMSO groups than in the control, DMSO, and AGOM groups. AGOM decreased LPO levels in the CMS+AGOM and AGOM groups ($p < 0.001$), although CMS did not affect LPO levels.

Discussion

The CMS paradigm as an animal stress model is well-known to induce anhedonia, anxiety-like, and stress symptoms in experimental animals. Consequently, it offers translational promise for the study of the neurological basis of stress (Willner 2016). This study demonstrated that therapy with AGOM reduced depression-like behaviors induced by CMS in rats. It was determined that the stimulation of TRPV1 activation increased the levels of $[Ca^{2+}]i$, caspase -3, caspase -9, LPO, and apoptosis in the hippocampus of the stress group, whereas the exposure to CMS decreased the cell viability levels of the hippocampal neurons. The TRPV1-mediated Ca^{2+} influx, oxidative stress (LPO), and apoptosis indicators (apoptosis, caspase -3, and caspase -9 levels) in the hippocampus were decreased by AGOM administration.

The antioxidant effects of melatonin and its effects on second messenger systems are well-known (Kahya et al. 2017; Cherngwelling et al. 2021). Agomelatine is also a melatonin-derivative. Its reducing effect on these values may have come from the fact that agomelatine is a derivative of melatonin which is an antioxidant. This issue needs to be investigated in future studies. Also, more thorough research is required to fully understand the connections between stress, oxidative stress, TRPV1, and apoptosis.

Acknowledgments

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Disclosure statement

The authors report no conflict of interest.

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Oral Presentations

Oral Presentation 3

An interaction between cisplatin-induced optic nerve injury and TRPM2 channel

Hatice DALDAL
Department of Ophthalmology, Faculty of Medicine, Uşak University, Uşak, Türkiye.

Cisplatin is used as an effective and common chemotherapeutic agent in the treatments of several cancer types. However, the treatment of cisplatin induces oxidant and apoptotic adverse actions in several neurons, including the optic nerve (Güçlü et al. 2018). In our body, several physiological processes such as mitochondrial and phagocytosis functions induce oxidative stress. Oxidative stress is induced by the excessive generation of reactive oxygen species (ROS). The treatment of cisplatin kills the cancer cells via the excessive generation of ROS, although the excessive generation of ROS was modulated by antioxidants such as resveratrol and curcumin (Özkaya and Nazıroğlu 2020; Agcayazi et al. 2021). It seems that the cisplatin treatment-induced excessive ROS production results in TRPM2 channel activation via the DNA damage and ADP-ribose production (Özkaya and Nazıroğlu 2020). In turn, TRPM2-mediated excessive Ca^{2+} influx in the optic nerve stimulates intrinsic apoptotic pathway and death receptor signaling (Güçlü et al. 2018). In the oral presentation, I will summarize the present literature results on the cisplatin-induced optic nerve injury and TRPM2 channel activation in rats.

The present literature results indicate that ROS-mediated TRPM2 activation has a main role in the cisplatin-induced optic nerve injury and apoptosis in rats, although the levels of injury and apoptosis were modulated by the treatments of antioxidants such as resveratrol and curcumin.

Key words: Apoptosis; Curcumin; Optic nerve injury; Oxidative stress; TRPM2 channel.

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Oral Presentations

Oral Presentation 4

Recent developments on the traumatic brain injury models in the experimental animals

Kemal ERTİLAV
Department of Neurosurgery, Faculty of Medicine, Suleyman Demirel University, Isparta, Türkiye

Traumatic brain injury (TBI), which is the leading cause of death worldwide, is caused by a number of traumatic circumstances, such as sports accidents or automobile accidents that inflict forceful impacts to the head. The surrounding soft and hard structures automatically protect the human brain from minor harm. Despite these safeguards, the brain can only withstand a certain amount of force, making it susceptible to damage from strong impacts (Ackermans et al. 2021).

By simulating injury at the molecular, cellular, and organismal levels in animals, the research of TBI has been greatly expanded. Models aim to evaluate the possibility of therapeutic intervention when this study enters a secondary phase with elongated and evolving secondary injuries (Weber et al. 2019). Early models looked at the biophysical aspects of TBI, while more recent research has concentrated on understanding how these injuries alter the molecular cascades. The three most popular injury simulations used in animal experiments; (1) the weight drop model is dropping a projectile of specified characteristics through a tube, (2) In the piston-driven closed head injury model, injury is caused by a piston, and the Maryland model, which simulates the impact of a steel ball rolling down a 2.1-meter track on an object (Bodnar et al. 2019).

I will discuss recent advancements in the traumatic brain injury models in the experimental animals during the oral session. We can greatly improve our understanding of the natural history of TBI by developing and characterizing novel models.

Key words: Brain; Traumatic brain injury; Rats.

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Oral Presentations

Oral Presentation 5

Involvement of TRPV1 channel in the etiology of epilepsy

Kaan ERBAKAN
Student, Faculty of Medicine, Ordu University, Ordu, Türkiye

Epilepsy is characterized as an acute transient complex neurobehavioral disorder affecting approximately 2% of the population worldwide. It's well known that a feature of epileptic activity is excessive synchronous neuronal activity via excessive calcium ion (Ca^{2+}) influx in the brain areas.

Transient receptor potential (TRP) super family has 30 members within 7 seven groups and they are calcium ion (Ca^{2+}) permeable cation channels. Activation and inhibition mechanisms of TRP superfamily is different from the voltage gated Ca^{2+} channels and ligand-gated ion channels. Some members of the TRP superfamily are activated by oxidative stress. TRP channels have physiological role in the mechanisms controlling several neurological diseases, including epilepsy.

A member of the TRP superfamily is TRP vanilloid 1 (TRPV1) channel is mainly expressed in hippocampus which is a main epileptic area in the brain. In the etiology of epilepsy, overproduction of reactive oxygen species (ROS) has a main role. TRPV1 is activated by several stimuli including capsaicin and ROS. The evidence for TRPV1 channel involvement in epileptic seizures has been indicated in a limited number of studies. Activation of TRPV1 channels caused overload of Ca^{2+} entry into hippocampal and dentate gyrus granule neurons and subsequent increase in action potential generation which has an important effect on induction of seizure in the neurons (Bhaskaran et al. 2010). It was reported that administration of TRPV1 channel blocker (capsazepine) into brain before seizure induction via pentylenetetrazol caused anti-epileptic action (von Rüden et al. 2014). Recently, antiepileptic actions of TRPV1 channel blockers in the hippocampus of pentylenetetrazol-induced epileptic experimental animals were reported (Nazıroğlu and Övey 2015). In the young speaker presentation, I will summarize current data on the TRPV1 in the epilepsy.

In summary, it seems that TRPV1 represent a novel pharmacological approach towards the development of new drugs for the treatment of epilepsy.

Keywords: Epilepsy; Seizure; TRPV1 channel; Oxidative stress.

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Oral Presentations

Oral Presentation 6

Does GSH depletion induce TRPM2 activation in neuronal cells?

Ramazan ÇINAR
Neuroscience Research Center (NOROBAM), Isparta, Türkiye

The transient receptor potential melastatin 2 (TRPM2) is a non-selective calcium (Ca^{2+}) permeable cation channel belonging to the TRP ion channel family. TRPM2 activation induced by oxidative stress causes an above-normal intracellular Ca^{2+} accumulation and cell death in various cell types including neurons. Added to the abnormal TRPM2 function is that it causes many neurological disorders, including ischemia, stroke, Alzheimer's disease, neuropathic pain, Parkinson's disease, and bipolar disorders. In addition to the researches determining the role of TRPM2 in the disease, it has been reported that while TRPM2, glutathione (GSH) deficiency causes neurodegenerative diseases with the increase of oxidant, inflammatory and apoptotic factors in neuronal cells with TRPM2 activation, these factors decrease with GSH treatment. Progress has been made in defining the physiological functions of TRPM2 in the brain. Progress has been made in expressing TRPM2's physiological functions in the brain. In this review, we summarize recent evidence on the role of TRPM2 in healthy and diseased neuronal cells and on the potential therapeutic effects of targeting TRPM2. Collectively, this review shows that TRPM2 represents a new prospective therapeutic target in neuronal cells.

Keywords; Neurodegenerative Disease; TRPM2 Channels; Apoptosis; Glutathione depletion, Oxidative Stress.

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Oral Presentations

Oral Presentation 7

TRP ion channels and approaches in COVID-19

Hatice Elif BABAYİĞİT[1], İbrahim KAMACI[1], Esin AKBAY ÇETİN[1]

[1]Department of Biology, Faculty of Science, Hacettepe University, Ankara, Türkiye.

Living systems have hundreds of ion channels on their surfaces. The TRP protein family defined in Drosophila is one of the channels providing ion passage and is present in living systems from simple organisms to complex. TRP channels have various roles in sensory systems and are located in almost all cells. TRP cation channels of mammals consist of seven subfamilies and each of them has their own structure, location etc. (Clapham, 2003). Since they play a role in sensory transmission, sciencists think that they could be potential targets for relieving the symptoms of various diseases (Miller, 2006).

COVID-19 disease caused by the SARS-Cov-2 virus occurs with symptoms such as headache, muscle pain, respiratory and digestive problems, and loss of taste and smell. TRP channels have been targeted in some approaches to reduce these symptoms. In some studies that blocked TRP channels, the symptoms were observed to disappear or to decrease significantly (Fernandes et al., 2012). The virus requires angiotensin converting enzyme 2 and transmembrane protease serine 2 proteins to enter host cells. These processes are mediated by endocytosis and by Ca^{+} flow. In this context, it has been observed that the blocking of TRP channels hinders the entry of the virus into the host.

The aim of this review is to examine the severe symptoms, the potential roles of TRP ion channels in the spread and progression processes of the COVID-19 pandemic, which led to a worldwide crisis, as well as their therapeutic approaches.

Keywords: TRP ion channels; COVID-19; angiotensin converting enzyme 2

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Oral Presentations

Oral Presentation 8

Early life stress and neuroinflammation

Gülin ÖZDAMAR ÜNAL
Department of Psychiatry, Faculty of Medicine, Süleyman Demirel University, Isparta, Türkiye

Genetic factors and early life events may interact with each other in a complex way during the developmental stages, leading to susceptibility to depression and vulnerability to environmental stress factors in the future. Early life stress is defined as traumatic life events from the prenatal period to adolescence. Early life is a critical and sensitive period to environmental influences, with long-term effects on behavioral, neuronal, and psychological development. Exposure to chronic and/or extreme stress early in life, when rates of synaptic regrowth and remodeling are high, has adverse effects on the developing brain. Studies in both animals and humans show that stress experienced in the early stages of development can cause permanent changes in the ability of the hypothalamic-pituitary-adrenal axis, abnormal immunological responses, and lasting changes in cellular, molecular, and epigenetic forms of plasticity, to respond to stress in adulthood and increase susceptibility to depression.

Stressful life experiences stimulate the immune system. Exposure to early life stress has been reported to be associated with higher proinflammatory cytokines and also a higher risk of mental illness in adulthood. Increasing cytokine levels induce changes in microglia, leading to structural and functional changes in the brain, and predisposing individuals to mental illnesses.

The relationship between early life stress and mental disorders, as well as the neurobiological mechanisms behind this interaction, will be the topic of conversation during this presentation. This presentation will provide additional information about the processes that lead to individual differences in the neurodevelopmental effects of early life stress experienced by individuals.

Keywords; Early life stress; Neuroinflammation; Mental disorders.

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Oral Presentations

Oral Presentation 9

Investigation of TRPM2 cation channel activation in PTZ-induced SH-SY5Y cells by patch-clamp technique: Regulatory role of valproic acid

Adem AHLATCI[1], Muhammet BEKTAŞ[1], Yasin TÜLÜCE[2], Kenan YILDIZHAN[3]

[1]Department of Biophysics, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye.

[2]Department of Medical Biology, Faculty of Medicine, Van Yuzuncu Yil University, Van, Türkiye.

[3]Department of Biophysics, Faculty of Medicine, Van Yuzuncu Yil University, Van, Türkiye.

Neurotoxicity is the event that neurons are damaged by natural or artificial toxic substances. Pentylenetetrazole (PTZ) is a neurotoxic substance and is used to produce experimental neurotoxicity. Transient Receptor Potential Melastatin 2 (TRPM2) Channel is a non-selective cation channel activated by adenosine diphosphoribose (ADPR), calcium ion (Ca^{2+}) and reactive oxygen species and nitrogen species. It is inactivated by N-(p-amylcinnamoyl) anthranilic acid (ACA). Valproic acid (VPA) is a short-chain fatty acid in the chemical structure of N-dipropyl acetic acid, it is used as various anticonvulsants and mood stabilizers, especially in psychiatric and neurological cases. Studies have shown that valproic acid blocks voltage-gated sodium or calcium channels (Bowden 2003), but its effect on the TRPM2 channel in the neuron cell line has not yet been clarified.

SH-SY5Y cells were divided into five groups; control, control + ADPR, PTZ (30 µM for 24 hours), VPA (1 mM for 24 hours), and PTZ + VPA (30 µM for 24 hours and 1 mM for 24 hours) (Taskiran et. al., 2021). The patch-clamp technique was used to observe the activation of the TRPM2 channel and the protective effect of VPA in the neurotoxicity model created by PTZ. In the study, ADPR was used as an agonist and ACA as an antagonist for TRPM2 stimulation in SH-SY5Y cells (Yıldızhan and Nazıroğlu 2020). The whole-cell mode patch-clamp record showed us that in the ADPR-stimulated groups, the intracellular Ca^{2+} flow was highest in the PTZ group compared to the other groups. While no intracellular Ca^{2+} flow was observed in the VPA group, intracellular Ca^{2+} flow was significantly inhibited in the PTZ+VPA group compared to the PTZ group.

In conclusion, in the electrophysiological study using the patch-clamp technique, we observed that VPA has a regulatory effect on TRPM2 channel currents in PTZ-induced SH-SY5Y cells.

Keywords: Epilepsy; TRPM2 channel: Valproic acid; Patch-clamp.

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Oral Presentations

Oral Presentation 10

Orthodontic teeth movement-induced pain and TRPV1 channel

Yener YAZĞAN
Department of Biophysics, Faculty of Medicine, Kastamonu University, Kastamonu, Türkiye

Pain occurs from several stimuli factors, including orthodontic treatment. Most of orthodontic treatments induce pain via inflammation, edema, ischemia and pressure in patients. Pharmacological and non-pharmacological methods can be relatively used in orthodontic pain management. Involvement of excessive Ca^{2+} influx in cytosol of neurons has been known for a long time. Intracellular Ca^{2+} concentration is increased activation of cation channels. One member of the cation channels is transient receptor family (TRP) superfamily. One member of TRP superfamily is TRP vanilloid 1. The TRV1 channel is activated by capsaicin, high temperature (43 °C ≥), acidic pH and oxidative stress (Hargreaves and Ruparel 2016). The channel is also activated by mechanical stimuli. Hence, TRPV1 mediates spontaneous pain and mechanical hyperalgesia in the orofacial muscle inflammation (Wang et al. 2019). Recent data indicated involvement of TRPV1 in the orthodontic treatments. In the presentation, I will review involvement of orthodontic teeth movement in the activation of TRPV1 channel in the several neurons.

In summary, it seems that orthodontic teeth movement induces pain via activation TRPV1 channel in neurons.

Keywords: Mechanical stimuli; Orthodontic teeth movement; TRPV1 channel; Pain

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Oral Presentations

Oral Presentation 11

Evaluation of the role of Radish (*Raphanus sativus*) extract in movement tests in MPTP-induced experimental Parkinson's model in Balb/C mice*

Sümeyye UÇAR[1], Harun ÜLGER[1], Özge AL[1], Gökçe Şeker KARATOPRAK [2], Zeynep YILMAZ[3], Füsun Ferda ERDOĞAN[4]

[1]Erciyes University, Faculty of Medicine, Department of Anatomy, Kayseri, Türkiye.
[2]Erciyes University Faculty of Pharmacy, Department of Pharmacognosy, Kayseri, Türkiye.
[3]Erciyes University, Faculty of Medicine, Department of Neurology, Kayseri, Türkiye.
[4]Erciyes University, Faculty of Medicine, Department of Medical Biology, Kayseri, Türkiye.

Parkinson's disease (PD) is neurodegenerative disease in the elderly population and is characterized by the degeneration of dopaminergic neurons (Liu et al. 2020). MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a selective neurotoxin that is used to induce PD in animal models (Haeri et al. 2019). Radish (*Raphanus sativus*) is a vegetable that contains various nutrients, vitamins and minarels as well as sulforaphene and flavanoid that have neuroprotective effects (Choi et al. 2020).

In this study, the protective effect of radish extract was investigated in male Balb/C mice exposed to MPTP. The animals divided to five groups, negative control and four experimentals. The experimentals animals received 30 mg/kg MPTP intraperitoneally for 5 days (positive control, radish, L-DOPA, radish+L-DOPA). After MPTP injections, open field test and pole test have done once a week for 4 weeks. The mean distance (cm) and speed (cm/s) of the groups were calculated with EthoVision XI open field software. The values of groups were 3846.03 and 14.61, 2233.98 and 7.86, 2353.02 and 8.92, 2657.86 and 10.14, 3235.79 and 11.51 respectively. It was determined that increase in the total distance traveled and speed Radish +L-DOPA group compared to the MPTP group ($p<0.05$).

In the pole test, the time (s) to downwards was calculated as in the groups 18.06, 93.35, 27.3, 25.85 and 24.33 respectively. It was decreased in Radish +L-DOPA compared to the MPTP group ($p<0.05$).

In the treatment of Parkinson's, it has been determined that the combined application of radish and L-DOPA with behavioral observational data is could more effective.

Keywords: Parkinson's disease, MPTP, Movement test, Locomotor activity, Radish, *Raphanus sativus*, L-DOPA.

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Poster Presentations

Poster No, 1

Probable pathways of SARS-CoV-2 to central nervous system

İbrahim KAMACI[1], Hatice Elif BABAYİĞİT[1], Esin AKBAY ÇETİN[1]

[1]Department of Biology, Faculty of Science, Hacettepe University, Ankara, Türkiye

Various reported cases related to the COVID-19 pandemic since 2019 has shown that SARS-CoV-2 directly or indirectly affects the nervous system besides the upper respiratory tract (Whittaker et al. 2020).

SARS-CoV-2 is a zoonotic strain of coronavirus with various structural proteins. It is reported that spike protein, which is one of its structural proteins, can bind to or interact with Neuropilin-1, CD147 (Basigin), KREMEN1, ASGR1 (Asialoglycoprotein Receptor), Furin, LRP1 (Lipoprotein Receptor-Related Protein 1) and Ephrin receptors as well as ACE-2 (Angiotensin Converting Enzyme-2) and TMPRSS2 (Transmembrane Serine Protease 2) receptors. The related studies suggest that these possible receptors in the target of SARS-CoV-2 cooperate with ACE-2, hence make the central nervous system an open target for the virus (Zalpoor et al. 2022).

The first possible route of SARS-CoV-2 is seen as the route from the olfactory epithelium to its bulb via the trigeminal nerve (CN V) and olfactory nerve (CN I) pathway. Additionally, the virus entering the bloodstream can reach the Blood Brain Barier, cross the barrier and spread to neurons through the oligodendrocyte in a process called “Trojen horse”. Lastly, another route considered focuses on the vagal nerves of the enteric system associated with the central nervous system (Guadarrama-Ortiz et al. 2020).

This literature review focuses on possible entry routes of SARS-CoV-2 into the nervous system. In this context, a route has been established based on the receptors in the nervous system cells, which are reported to be the target of SARS-CoV-2, based on the studies.

Keywords: SARS-CoV-2; Neuropilin-1; KREMEN1; ASGR1; Trojen horse

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Poster Presentations

Poster No, 2

Low molecular weight heparin treatment reduced apoptosis, oxidative stress, and calcium signaling in the thrombocytes of patients with recurrent pregnancy loss and thrombophilia: Involvements of TRPM2 and TRPV1 channels

Yusuf DAL[1], Mustafa NAZIROĞLU[2,3], Mehmet Okan ÖZKAYA[1]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Süleyman Demirel University, Isparta, Türkiye

[2]Neuroscience Research Center, Suleyman Demirel University, Isparta, Türkiye

[3]Department of Biophysics, Faculty of Medicine, Suleyman Demirel University, Isparta, Türkiye

We hypothesized that the cytosolic Ca^{2+} ($cytCa^{2+}$) concentration regulator properties of low molecular weight heparin (LMWH) may affect $cytCa^{2+}$ concentration via modulation of TRPM2 and TRPV1 in thrombocytes of patients with recurrent pregnancy loss (RPL). The objective of this study was to investigate the effects of LMWH on calcium signaling, oxidative stress, and apoptosis in the thrombocytes of RPL patients.

Thrombocyte and plasma samples collected from ten patients with RPL and ten healthy controls were used in the study. The $cytCa^{2+}$ concentration, cytROS, mitochondrial membrane depolarization, apoptosis, caspase 3, and caspase 9 values were high in the plasma and thrombocytes of RPL patients, although they were diminished by the treatments of LMWH, TRPM2 (ACA) and TRPV1 (capsazepine) channel blocker. After LMWH treatment, the cell viability level was increased in the thrombocyte of RPL patients.

In conclusion, the current study results suggest that the treatment of LMWH is useful against apoptotic cell death and oxidative stress in the thrombocytes of patients with RPL, which seem to be dependent on increased levels of $cytCa^{2+}$ via the activation of TRPM2 and TRPV1.

Keywords: Recurrent pregnancy loss; Low molecular weight heparin; Apoptosis; Calcium signaling; Oxidative stress; Thrombocytes.

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Poster Presentations

Poster No, 3

Investigation of frequency and diversity of experimental animal models of schizophrenia

Ferruh KARAMANGİL
Department of Pharmacology, School of Medicine, Ondokuz Mayıs University, Samsun, Türkiye

Developing reliable, predictive animal models for complex psychiatric disorders such as schizophrenia is essential to increase our understanding of the neurobiological basis of the disorder and to develop new drugs with improved therapeutic efficacy. The aim of this study is to scan the experimental schizophrenia models in the literature and evaluate them as models, dates, and numbers.

The research was carried out using the Pubmed database. While searching the database, the terms "Schizophrenia and/or animal, mouse, rat, genetic/chemical and behaviorally-induced" were used.

The data obtained as a result of the scanning were classified categorically according to the model, experimental animal and year results. Each category was divided into subcategories and compared statistically in terms of the model that were used.

According to the results obtained from Pubmed database, it was seen that 44.13% of the 12150 experimental animal studies were performed with mice and 55.86% with rats. It was found that 4.94% of studies with mice were chemically induced, 4.13% were created in transgenic models, and 90% were created by behavioral and other methods (Jones et al. 2011). It was found that 27.72% of studies with rats were chemically induced, 19.15% were created in transgenic models, and 53.11% were created by behavioral and other methods (Chambers and Self 2002; Alquicer et al. 2008). As a result of the comparison of the models used with the subgroups, it was found that the method and the experimental animal strain were statistically significant ($p<0.001$). In addition, as a result of the analysis made with the chi-square test, it was found that each scanning title used and the methods used throughout the year were statistically significant between mice and rats ($\chi 2=35.84$, 6, $p<0.001$).

Our results showed that a significant majority of the schizophrenia model used in the studies was created by behavioral methods. In addition, while behavioral methods are used in mice, it is seen that models induced by various chemicals are more common in rats. It is understood that the use of transgenic studies in recent years with developing biotechnological methods has increased the frequency of use in experimental animal models of schizophrenia and future studies will be in this direction.

Keywords: Schizophrenia, experimental animal models, mouse, rat.

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