24th World Congress on
Pharmacology
&
7th World Heart Congress
August 19-20, 2019 Vienna, Austria

Keynote Forum
Day 1

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Mulkijanyan Karen

Tbilisi State Medical University, Georgia

Steroidal compounds of vegetable origin in treatment of circulatory disorders

Modern pharmacy pays a special attention to the development of vasoactive anti-inflammatory drugs free of unwanted side effects that characterize the majority of currently available corticosteroids and NSAIDs.

The presented study aimed to determine specific pharmacologic properties of spiro- and furostanol type steroidal glycosides obtained from the Butcher's broom (*Ruscus ponticus L.*) and estimate their possible mechanism of action.

Assessment of the specific anti-inflammatory activity of RE on "granuloma pouch" model revealed that it caused statistically significant ($p < 0.001$) difference both in exudate volume and mass of dried granuloma. Further investigation on the formalin-induced rat paw edema confirmed the anti-exudative activity of RE. As the observed effect can be conditioned by several reasons including the change in the diameter of blood vessels, stimulation of α-adrenoreceptors or blocking the release of histamine and bradykinin, more detailed study of the mechanism of action of RE, a series of experiments were conducted, using vital dyes Evans blue (EB) and sodium fluorescein (SF). In intact animals SF after intravenous administration rapidly permeates into all organ tissues in contrast with EB, which does not leave the blood vessels.

Subcutaneous administration of SF and EB on the background of adrenalin or histamine altered the shape of SF pharmacokinetic curve reflecting the vasotropic effects of the agents, whereas for EB it remains unchanged. RE does not change the Tmax of SF, but the concentration of the dye increases. No alterations are observed for EB.

In *in situ* experiments it was found RE causes the constriction of the mice mesenteric vessels along with increased blood flow. Moreover, RE neutralizes effects of histamine, probably due to stimulation of α1-adrenoceptors.

Finally, it was found, that both prazosin (α1-blocker) and diltiazem (Ca^{2+} channel blocker) decrease the contractility of isolated femoral vein rings caused by RE, suggesting that observed vasotropic effects of RE are mediated by stimulation of vascular adrenoreceptors along with the simultaneous increase of Ca^{2+} in vascular endothelium.

Assessment of safety of RE in chronic 90-day experiment revealed the absence of any toxic effects on major systems.

Summarizing the obtained data, it may be concluded that the studied RE can be considered as prospective candidate for the development of anti-inflammatory vasoactive remedy free of toxic/side effects.

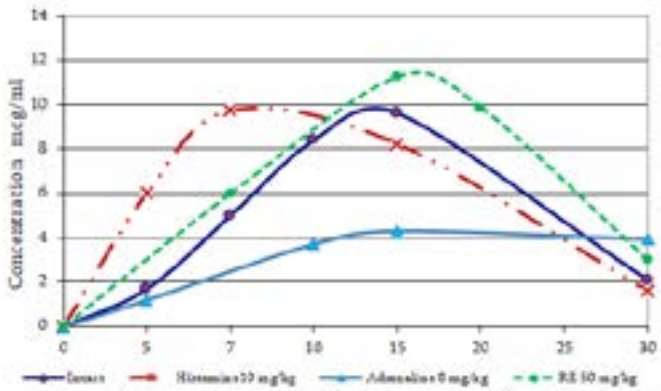

Figure: Pharmacokinetics of SF on the background of different vasotropic agents: x-axis - time (min)

Recent Publications

1. Khubulava S, Chichiveishvili N, Mulkijanyan K et al. (2019) Effect of high dose of selenium nanoparticles on alimentary tract in rodents. J Nanomed Nanotechnol, 10(2):531-537.
2. Mulkijanyan K (2018) The pharmacological potency of plant polymers in the prevention/treatment of peptic gastric ulcer. J Forensic Toxicology & Pharmacology 7:28.
3. Gokadze S, Mulkijanyan K et al (2017) Formulation and technology development of herbal phenolic biopolymer-containing films for burn treatment. Georgian Medical News, 6(267):119-124.
4. Taylor BJ, Mulkijanyan KG (2016) An overview of laboratory animal science in the nation of Georgia. Lab Animal 45(11):415-417.
5. Mulkijanyan K et al. (2015) Plant biopolymers from Boraginaceae family species and their synthetic derivatives: prospective pharmacological agents. Clinical & Experimental Pharmacology, 5(4):46.

Biography

Karen Mulkijanyan heads the Department of Preclinical Pharmacological Research at Tbilisi State Medical University Institute of Pharmacochemistry and is full Professor at Caucasus International University Faculty of Medicine. He holds MS in Biochemistry and PhD in Pharmacy. His research interests cover the experimental pharmacology; toxicology of natural products; analysis of structure-activity relationship (SAR) and prediction of bioactivity of natural, modified and synthesized compounds; IP protection; technology transfer and commercialization; use and care of laboratory animals. K. Mulkijanyan was a manager/key investigator of fundamental and applied research projects funded by CRDF Global/GRDF (2007-2014), STCU (2011), GNSF/SRSNF (2009-2018) and co-authored 120+ publications in peer-reviewed journals, 40+ presentations and 2 patents in pharmacology. As Organizing Committee Member, he arranged over 15 international events on pharmacology/toxicology. He is on the editorial boards of several journals in pharmacology/toxicology. In 2015 K. Mulkijanyan founded and is a President of the Georgian Association for Laboratory Animal Science.

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Shanaz Tejani-Butt

University of the Sciences, USA

Relevance of animal models in affective disorders research

According to the World Health Organization, mental disorders are one of the leading causes of disability in the US and worldwide. However, several challenges exists in the treatment of these disorders. First of all, diagnosis is difficult, especially in the young and the elderly, and the course of the disease can get complicated when the patient suffers from additional chronic conditions. Secondly, even when appropriate medications exists, a large number of patients do not receive treatment or are found to be treatment resistant. Thirdly, the neurochemical basis underlying the pathophysiology of the disorders is not well known, and our current understanding of these disorders is largely based on animal models.

Exposure to stress triggers a complex array of physiological, behavioral and neurochemical processes in order to promote homeostatic adaptation to the stressful stimuli. Repeated and chronic stressors pose a risk for psychiatric ailments, affecting our daily performance, and leading to a high public health burden. Appropriate animal models are therefore required for exploring the underlying neural mechanisms of stress, and for the screening of new therapeutic agents.

We and other researchers have reported on the use of the Wistar-Kyoto rat strain in the study of several neuropsychiatric disorders. When Wistar-Kyoto rats are exposed to stress stimulation, they respond with behaviors that resemble human depressive behaviors, such as anhedonia, psychomotor retardation, ambivalence and negative memory bias. Following stress manipulations and treatment, autoradiography analyses have revealed significant alterations in neurotransmitter receptors in limbic brain regions.

This presentation will review the utility of the Wistar-Kyoto animal model for furthering our understanding of the pathogenesis of affective disorders. Although potential problems and limitations exists in translating animal findings to human conditions, such comparisons are necessary for advancing our understanding of the mechanisms, and for developing improved interventions for these disorders.

Biography

Shanaz Tejani-Butt is a Professor in the department of Pharmacology and Toxicology at the University of the Sciences in Philadelphia. Dr. Tejani-Butt's research interests include the neurobiological mechanisms associated with the regulation of biogenic amines in an animal model of depressive behavior, implications of these biogenic amines in modulating stress and reward, and therapeutic action of psychiatric drugs. Dr. Tejani-Butt has been a recipient of numerous research grants, and served as a Grant Reviewer for the National Institute of Health. Shanaz Tejani-Butt received her PhD in Medicinal Chemistry from the Medical College of Virginia, her MS in Organic & Natural Product Chemistry and BS in Chemistry and Microbiology from the University of Bombay. She received her MBA degree in Healthcare Business from the Mayes College of the University of the Sciences.

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Samir Morcos Rafla

Alexandria University, Egypt

The significance of early repolarization and incomplete right bundle block in athletes

Introduction: Sudden death in athletes is a major concern; the predictors and value of prior investigations remain to be settled. Of the electrocardiographic (ECG) findings in athletes is early repolarization, its incidence and significance is the subject of this work.

Methods: The study included hundred persons engaged in competitive sports for duration not less than six months; with training at least three days per week and at least two hours per day. All were males. Collection of cases started March till December 2015. Full history especially questioning for syncope, tachycardia or chest pain was obtained as well as family history of sudden death or coronary disease; examination for BP, any cardiac murmurs or arrhythmia. ECG was done for all plus echo Doppler in some cases. Early repolarization was accepted present if J point is elevated more than one mm in LII, III, aVF or in chest leads, raised ST>1mm. RV conduction disturbance was considered present if there is Rsr' or bifid R. Minor or minimal changes were not counted.

Results: During the period from 1/1/2015 to 1/10/2016, 100 athletes were screened by ECG, 54 played isotonic sport while 46 were on isometric sport. Types of sports: 46 isometric (static) (body builders). Isotonic (dynamic) 54 (Bicycling 6, Football 15, Tennis 3, Basketball 16, Volleyball 8, Swimming 4, Boxing 2) . Echo was done in 15, increase in LV size was found in 5 (Diastolic diameter up to 61mm). Follow up by telephone questionnaire was done for most of the subjects. 10 persons were re-examined after months, no abnormal events were found. 23 had either or both abnormalities. Early repolarization was found in 19 and Rsr' were present in 9 subjects (5 had both). None was diagnosed as Brugada or RV dysplasia. Follow up by telephone was up to two years. Of the 23 subjects 2 could not be reached (no answer) and in 2 the telephone was wrong. No one reported tachyarrhythmia or syncope neither before recruitment in the study (retrospective) or after follow-up (prospective).

Conclusion: Early repolarization and RV conduction disturbance did not prove to be hazardous.

Biography

Samir Rafla is a Professor of Cardiology at Alexandria University, Department of Cardiology. He is the Head of the Cardiology Dept. Alexandria University from 2004 till August 2007. He got a Bronze medal for Bachalorious with honor 1970; Silver medal: Award for scientific encouragement at Alexandria University in 1994. He has won the Award of the Egyptian Medical Syndicate Feb 2008 for scientific distinction.

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Shirley Taniguchi

University of São Paulo, Brazil

Pharmacological advice for clinical practice

Statement of the Problem: Treating drugs symptomatically, reversing drug side effects without considering the receptors involved, and combining drugs without following specific criteria, may result in inefficient attempts to resolve clinical events.

Methodology & Theoretical Orientation: This was a retrospective survey of patients hospitalized in a large general hospital located in the city of São Paulo (Brazil) and individual patients treated at several hospitals in the region.

Findings: Difficult to control bleeding may occur with the administration of cardiotonic agents (phosphodiesterase inhibitors) in patients submitted to surgery. Combining anticoagulants with drugs with a high albumin binding rate may also cause significant bleeding. blockers such as phenytoin without accompanying cardiac function may Intravenous administration of voltage-dependent sodium channel lead to arrhythmia and difficult to reverse cardiac arrest

Administering depressant drugs to contain akathisia caused by neuroleptics may result in a significant reduction of consciousness levels. Treating immediate postoperative period opioid hallucinations with typical neuroleptics may cause motor agitation that could significantly affect the surgical procedure.

Treating L-Dopa hallucinations with neuroleptics may cause motor side effects contributing to the motor difficulties associated with Parkinson's disease.

Treating confusion with neuroleptics may increase the motor side effects associated with the use of central acting anticholinesterase inhibitors or cholinergic agonists in patients with Alzheimer's disease.

Conclusion & Significance: An individualized medical prescription should contain drugs selected based on their mechanism of action, half life, albumin binding rate, and predicted side effects. This would help reduce risks and increase the chances of therapeutic success.

Biography

Shirley earned her M.S. in Pharmacology at the University of São Paulo in 1993. From 1994-1996, she worked as a researcher for the Japanese Ministry of Education in the Department of Pharmacology at the University of Kitasato in Tokyo. She has been an instructor in Pharmacology since 1997 and a researcher at the Medical School at the University of São Paulo (Faculdade de Medicina /Universidade de São Paulo). Shirley has been teaching undergraduate Pharmacology classes within Healthcare courses under the theme 'Education to Prevent the Misuse of Drugs'.Her assistance is requested whenever there is difficulty associated with the pharmacological treatment in any given sector within different hospitals. Through research projects registered with the Ministry of Health, Shirley accesses and analyzes medical records to propose pharmacological care to complement patients' treatments and minimize risks. Shirley has assisted in research with drugs in the Intensive Care Unit, Urgent Care, sedation in oncology, and in Psychiatry, Geriatrics and Pediatrics departments.

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Day 2

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Jahanshah Amin

University of South Florida, USA

A ketoxime analogue of ketamine with distinct molecular actions on GABAA and NMDA receptors demonstrates superior antidepressant activity

Dissociative anesthetic ketamine can rapidly alleviate symptoms of psychiatric depression with prolonged duration of action. Despite the promise, untoward psycho-mimetic manifestations of ketamine have curbed its clinical application. In a search for a ketamine substitute with higher antidepressant activity and lower side effects, we synthesized several novel ketamine analogs and tested them *in vitro* and *in vivo*. A ketoxime analog, termed oximeamine, shows the following pharmacological properties compared to ketamine: First, oximeamine potentiates the activity of $GABA_A$ receptors, specifically that of cerebellar $\alpha_6\beta_2\delta$ subtype, with higher potency. Second, oximeamine blocks NMDA receptors with similar potency and efficacy yet associates with (on-rate) and dissociates from (off-rate) the NMDA receptors at a significantly faster rate. The relatively faster on- and off-rate of oximeamine appears most prominent at the NMDA NR1/NR2B receptor subtype. Third, neither oximeamine nor ketamine display any significant action on AMPA receptor subtypes. Finally, in forced swim test, oximeamine demonstrates a significantly greater antidepressant activity than ketamine. In conclusion, the differential yet lower intensity block of the NMDA receptor subtypes and the higher activity on the GABAA receptors, together with the more robust antidepressant activity herald the superiority of oximeamine over ketamine with higher antidepressant efficacy and lower side effects.

Recent Publications

1. Walters RJ, Hadley SH, Morris KDW, and Amin J: Benzodiazepines act upon $GABA_A$ receptors via two distinct and separable mechanisms. (2000) Nature Neuroscience; 3(12): 1274-1281.
2. Hevers W, Hadley SH, Lüddens H, Amin J: Ketamine, But Not Phencyclidine, Selectively Modulates Cerebellar $GABA_A$ Receptors Containing α_6 and δ Subunits. (2008) Journal of Neuroscience 28(20): 5383-5393.
3. Morris KW and Amin J: Insight into the mechanism of action of neuroactive steroids. (2004) Mol Pharmacol; 66:56-69.
4. Hadley SH & Amin J: Rat $\alpha_6\beta_2\delta$ $GABA_A$ receptors exhibit two distinct and separable agonist affinities. (2007) Journal of Physiology 581.3:1001-1018.
5. Amin J, Subbarayan MS. Orthosteric-versus allosteric-dependent activation of the GABAA receptor requires

numerically distinct subunit level rearrangements (2017). Scientific Reports 7 (1), 7770, 1-16.

Biography

J Amin laboratory has a primary interest in GABAA and NMDA receptor-channels. We have studied the structure/function relationship of subtypes of GABAA receptors to enhance our understanding of the molecular mechanism of action of sedative/hypnotic drugs. By co-expression of wild-type with anesthetic-sensitive subunits of GABAA receptors, we have determined the minimal number of subunits required for orthosteric- versus allosteric-dependent activation of GABAA receptor channels. The laboratory is also focused on drug discovery with particular interest in ketamine. In the last several years, we have synthesized a number of ketamine analogues and characterized their molecular actions on the NMDA and GABAA receptors. One oxime analogues of ketamine has shown great promise in terms of molecular signature on NMDA and GABAA receptors and in an animal model test for antidepressants.

Notes:

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Naranjan S Dhalla

University of Manitoba, Canada

Antiplatelet agents as a novel therapy of heart failure due to myocardial infarction

Background: Although different antiplatelet agents are used for the prevention of thrombosis and treatment of ischemic heart disease, very little information regarding therapeutic potential of these agents in heart failure is available.

Objectives: We have investigated the effects of some antiplatelet agents such as sarpogrelate (SAR) and cilostazol (CIL) treatments on cardiac dysfunction, cardiac remodeling and subcellular defects in heart failure due to myocardial infection.

Methods: Heart failure in rats was induced by including the coronary artery for 8 weeks and the drug treatment was started 4 weeks after inducing myocardial infarction.

Results: Marked depression in cardiac output and ejection fraction as well as increases in heart rate, left ventricle (LV) thickness and LV volume in the infarcted animals were attenuated by SAR and CIL. Alterations in myofibril Ca^{2+}-ATPase, as well as myosin isozyme contents and gene expression in the failing heart were reduced by SAR and CIL. Likewise, changes in sarcoplasmic reticular Ca^{2+}-uptake and release activities, Ca^{2+}-pump and Ca^{2+}-release protein content as well as their mRNA levels were attenuated by both drug treatments.

Conclusions: These results provide evidence that both SAR and CIL delay the progression of heart failure and improve cardiac function by attenuating cardiac remodeling, subcellular defects and abnormalities in cardiac gene expression. It is suggested that antiplatelet agents may prove to be a viable therapy for the treatment of heart failure. (Infrastructure support for this study was provided by the St. Boniface Hospital Foundation)

Recent Publications

1. Dhalla N S, Takeda N, Rodriguez-Leyva D and Elimban V (2014) Mechanisms of subcellular remodelling in heart failure due to diabetes. Heart Fail Rev 19(1):87-99.
2. Dhalla N S, Rangi S, Babick A P, Zieroth S and Elimban V (2012) Cardiac remodeling and subcellular defects in heart failure due to myocardial infarction and aging. Heart Fail Rev 17(4-5):671-681.
3. Machackova J, Sanganalmath S K, Elimban V and Dhalla N S (2011) β-adrenergic blockade attenuates cardiac dysfunction and myofibrillar remodeling in congestive heart failure. J Cell Mol Med 15(3):545-554.
4. Dhalla N S, Saini-Chohan H K, Rodriguez-Leyva D, Elimban V, Dent M R and Tappia P S (2009) Subcellular remodeling may induce cardiac dysfunction in congestive heart failuren. Cardiovasc Res 81(3):429-438.

Biography

Naranjan S Dhalla is a Distinguished Professor and Director of Cardiovascular Developments, St. Boniface Hospital Albrechtsen Research Centre, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, and Winnipeg, Canada.