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TRACK 2

ADVANCES IN PHARMACOLOGICAL TOXICOLOGY

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SESSION CHAIR : **DR. BRAJADULAL CHATTOPADHYAY**
Jadavpur University, Kolkata, India

SESSION CO-CHAIR: DR. ANSHOO GAUTAM
Pharmacology and Toxicology Division, Defence Research and Development Establishment, MP, India

SESSION INTRODUCTION

TITLE: MUSCARINIC RECEPTOR 1 AGONIST ACTIVITY OF NOVEL ARECOLINE DERIVATIVES IN ALZHEIMER'S DEMENTIA MODELS

DR. KANCHUGARAKOPPAL S. RANGAPPA, DOS in Chemistry, University of Mysore, India

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DR. M H PIPELZADEH, Ahvaz Jundishapur University of Medical Sciences, Iran

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DR. KRISHNA CHATTOPADHYAY, Department of Chemical Technology, University of Calcutta, India

TITLE: RECENT ADVANCES IN DRUG DISCOVERY AGAINST SULPHUR MUSTARD INTOXICATION

DR. ANSHOO GAUTAM, Pharmacology and Toxicology Division, Defence Research and Development Establishment, MP, India

COFFEE BREAK & POSTER SESSION

TITLE: AMELIORATION OF CURCUMIN OF NICOTINE INDUCED NECROSIS OF DIFFERENT TISSUES OF FEMALE RATS IN PROTEIN RESTRICTED CONDITION

DR. BRAJADULAL CHATTOPADHYAY, Jadavpur University, Kolkata, India

TITLE: A NEW FRONTIER ON TOXICOLOGICAL STUDIES ON CENTRAL NERVOUS SYSTEM

DR. SANJITHA DAS, Department of Pharmaceutical Technology, Noida Institute of Engineering and Technology, India

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Amelioration of Curcumin of Nicotine Induced Necrosis of Different Tissues of Female Rats in Protein Restricted Condition

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Uses of different forms of nicotine (smoking and smokeless tobacco products) have been a major public health issue for many years. It is related with several cancers, cardiovascular disorder and many other diseases. Low dietary protein possesses a constraint on the metabolic activity and results in impaired detoxification machinery. The adverse effects of nicotine on different organs under protein restricted condition are still unclear. This study was performed to investigate the ameliorative effect of curcumin against nicotine induced changes in different tissues under protein restricted condition. Albino-rats were maintained under normal/protein-restricted diets and subcutaneously injected with nicotine tartrate (2.5 mg/kg body weight/day) and orally supplemented with curcumin (80 mg/kg body weight/day) for 21 days. The effects of the drugs were monitored by comet assay, UV-visible and CD-spectroscopy, and molecular docking. Cytokine profile and gene expression studies were performed by ELISA and Real-time-PCR respectively. Nicotine binds to DNA and distorts its structure at low concentrations and induces strand breaks at high concentration (>1mM). Curcumin revives nicotine induced structural changes of DNA. Nicotine elevates IL-6, TNF-α and STAT3 expression more in protein restricted condition and enhances p65 and Bcl-2 expression more in normal condition. Over-expression of antiapoptotic protein and DNA structural alteration by nicotine in normal diet condition indicates higher chances of malignant transformation of cells, whereas extensive DNA damage and inflammatory responses in protein restricted diet indicates cell-necrosis. Curcumin effectively ameliorates nicotine induced changes in both dietary conditions.

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Recent Advances in Drug Discovery Against Sulphur Mustard Intoxication

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Sulphur mustard (SM) is one of the most important blistering and vesicating agents. It is a chemical weapon of choice by the military and the terrorist groups, due to its prolonged action it produces mass casualties requiring prolonged and intensive care. The most common complications of SM occur in lungs, skin and eyes which are the principal target organ due to its direct effect. Despite rigorous research efforts on the antidote development to SM, employing a variety of *in vivo* and *in vitro* systems and using various mustard agents so far no satisfactory and recommended treatment has evolved. In view of the possible threat from various sources against the military and civilian populations, and the risk during the destruction of stockpiled mustard agents, development of a suitable antidote is prime requirement. The physicians should also be aware of the mass casualty due to SM exposure should be knowledgeable about the various medical countermeasures. In this chapter the various antidotes and treatment regime experimented in animal models and the treatment regimens recommended in human casualties are reviewed.

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Comparative Study of the Antioxidative Activity of Sesame Lignans and Conjugated Linolenic Acid Against Nicotine Toxicity

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Tobacco is a greater cause of death and disability than any other single disease. India is the 3rd largest tobacco producing country after USA and China. Use of different forms of tobacco is increasing day by day. Nicotine, the acute acting pharmacological agents of tobacco, plays the major role for drug of addiction. Elucidation of the complex effect of nicotine has worldwide implications. Nutritional status alters the actions, potencies and detoxification of toxicants. Any strategy through natural diet that prevents or slows the progression and severity of nicotine toxicity has a significant health impact. Nicotine induces oxidative stress. In search for natural antioxidants, present study was undertaken to evaluate the antioxidant efficacy of sesame lignans and conjugated linolenic acid, in nicotine treated rats. Experiments were conducted on male albino rats (120 – 130 g body weight) by injecting nicotine tartrate (3.5 mg/kg body wt. /day for 15 days) subcutaneously and thereby supplementing sesame lignans (0.2 g/100 g diet) and conjugated linolenic acid (0.2 g/100 g diet) orally to them simultaneously. Results showed that serum and liver lipid profile, activities of antioxidant enzymes, lipid peroxidation altered significantly due to oxidative stress generated by nicotine. Supplementation of sesame lignans and conjugated linolenic acid attenuates all the altered parameters by their antioxidant property. Results also showed that antioxidant activity of conjugated linolenic acid was more prominent than that of sesame lignans.

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Muscarinic Receptor 1 Agonist Activity of Novel Arecoline Derivatives in Alzheimer's Dementia Models

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The cholinergic deficit in Alzheimer's disease (AD) patient's brain has intensified research efforts to test cholinomimetic approaches for efficacy in AD therapy. Various therapies may be of potential clinical use in AD. Among these are cholinergic agents including muscarinic agonists, acetylcholinesterase inhibitors, and acetylcholine releasing agents. One of the muscarinic agonists tested in AD is arecoline and its bioisosters, which are widely, explored as muscarinic receptor 1 agonist (M1 receptor agonist) in AD research. In this regard, we have synthesized five and six membered heterocyclic ring system attached arecoline basic nucleus (*N*-methyl tetrahydropyridines) at 3rd position. Subsequently the synthesized arecolines derivatives were subjected to *in vitro* muscarinic receptor 1 binding affinity studies using male wistar rat brain synaptosomal membrane (cerebral cortex) and also cell line culture studies and extended this *in vitro* studies to *in vivo* pharmacological evaluation of memory and learning in male wistar rats (Rodent memory evaluation, plus and Y maze studies). Some of our synthesized molecules have shown very potent M1 receptor agonist activity and significantly elevated the basal IP3 levels in vitro and also have decreased beta-amyloid ($Abeta_{40}$ and $Abeta_{42}$) deposition in cell lines culture. These molecules have also shown very good antidementia activity in rat dementia model. Conclusions: Molecules with electron donating group as a substitute, has shown very good affinity towards the M1 receptor in vitro and has also elicited beneficial effects in vivo memory and learning models.

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An Eight year Experience upon Toxicological Properties of Hemiscorpius Lepturus Scorpion

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A lot of anxiety and expenses are faced annually because of *Hemiscorpious lepturus* (Farzanpay, 1987) scorpion envenomation among both adult and children in Khozestan province. This scorpion is endemic in Khozestan province and other south-western areas of Iran. The aim of the present report is to present data on the toxicological manifestations of the venom form this dangerous and unique scorpion. Special focus will be made upon the experimental findings both under *in vivo* and *in vitro* as well as on the pharmacokinetic and pharmacodynamics effects of this venom and its available antivenin. Possible implications in clinical setting will be highlighted.

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A New Frontier on Toxicological Studies on Central Nervous System

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After gaining relevant information on the harmful effects of a compound, the levels for its safe usage or the degree of its safeness is established. A wide range of toxicological studies are being undertaken as per national and International guidelines. Out of which the toxicological studies on Central Nervous System becoming the area of attraction. The present study highlights the possible CNS toxicities with a drug entity and their prevention and treatment. Fluoroquinolones can induce a wide range of serious adverse psychiatric effects showing depressant activity on the CNS. Its concomitant use of NSAIDs may increase seizure risk. Neurologic complications of cancer therapy are an increasingly important concern in patient management. Prompt recognition of these problems and their causes will have an impact on patient care in all areas of oncology. It is not surprising that clinical trails evaluating Biological Response Modifiers have also demonstrated that CNS toxicity is very common. The role of amifostine (WR-2721) in ameliorating radiation-induced central nervous system (CNS) toxicity is effective. Greater awareness of severe and complex CNS neurotoxicity even with low dose Cyclosporin A treatment in rheumatoid arthritis is of the utmost importance and so with Ciprofloxacin. Central nervous system (CNS) toxicity of tricyclic antidepressants (TCAs) is serious, costly, frequent, and difficult to diagnose early in its course. CNS lidocaine toxicity is biphasic and the most common cause for it is dosing error. This study concludes that the CNS toxicological studies of any new chemical entity will lead to its better use for the ailment of different diseases of mankind. Additional studies are warranted to investigate the protective effect with differing regimens of administration, more clinically relevant fractionation regimens and longer follow-up.

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Biochemical and Immunological Basis of Silymarin, a Milk Thistle (Silybium Marianum) Against Ethanol-Induced Oxidative Damage

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The metabolism of ethanol gives rise to the generation of excessive amount of reactive oxygen species and is also associated with immune dysfunction. We examined the efficacy of silymarin on the immunomodulatory activity and vascular function in mice with liver abnormalities induced by chronic ethanol consumption by measuring the protein, liver-specific transaminase enzymes, antioxidant enzymes and non-enzymes such as reduced glutathione (GSH) content, thiobarbituric acid reactive substance (TBARS) level, nitrite level, and activities of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GPx) and glutathione-S-transferase (GST), and cytokines such as interleukin (IL)-2, IL-4, IL-10, tumor necrosis factor (TNF)-α, gamma interferon (IFN-γ), vascular endothelial growth factor (VEGF)-A and transforming growth factor (TGF)-β1 in mice blood. Ethanol (1.6 g/kg body wt/day) exposure for 12 wks significantly increased TBARS and nitrite levels and GST activity, and significantly decreased GSH content and the activities of SOD, CAT, GR and GPx in whole blood hemolyzate of 8-10 wks-old male BALB/c mice (weighing 20-30 g). Ethanol exposure also elevated the activities of transaminase enzymes (AST and ALT), IL-10, TNF-α, IFN-γ, VEGF-A and TGF-β1, while decreasing the albumin concentration and IL-4 activity in the serum. Silymarin treatment significantly reduced AST, ALT, GST, IL-10, TNF-α, IFN-γ, VEGF-A and TGF-β1 activities and levels of TBARS and nitrite, and elevated albumin content, GSH level and activities of SOD, CAT, GR and GPx, compared to ethanol-treated group. The results suggests that silymarin can effectively ameliorate ethanol-induced oxidative challenges, immunomodulatory activity and angiogenesis processes.

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Inhibitors of Caspases as New Therapeutic Agents

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Caspases are diverse group of enzymes involved in apoptosis and inflammation. Activation of caspases contributes to large number of pathological conditions a) Apoptic disorders such as myocardial infarction, lung diseases, liver diseases and neuronal diseases b) Inflammatory disorders such as rheumatoid arthritis, osteoarthritis, gout and psoriasis. Inhibition of caspase activity is therapeutically effective in these disorders. Active site structure based approach, Structure activity relationship (SAR) based approach, peptidomimetics, high trough put screens (HTS) and fragment based approach teethering are currently used to discover caspase inhibitors. Caspases are cysteine proteases containing cysteine at active site and cleaves-D(Asp)-X-bonds. Active site cysteine and nearby histidine forms catalytic diad. Binding of negatively charged aspartic acid moiety of the substrate is favoured by positively charged arginine and glutamine. Catalysis of peptide bond cleavage by caspase involves formation of tetrahedral transition state thio hemi katal initiated by active site cysteine acting as nucleophile. Near by histidine residue aids product release. Inhibition by reversible inhibitors involves formation of thio hemi katal similar to tetrahedral transition state analog of substrate. A reversible caspase inhibitor pralancasan (VX-740) is discovered by active site directed approach. Clinical trials show that pralancasan is an effective anti inflammatory drug. Irreversible caspase inhibitors forms thio ether adduct resulting in inactivation of enzyme. An irreversible peptidomimetic inhibitor emricasan (1DN-6556) is designed from di peptide backbone which is effective in apoptic driven disorders. Isatins, a group of small molecule inhibitors are identified by high through put screens. Isatins contains a carbonyl group which is critical for inhibitory activity. Caspases are inactivated due to interaction of carbonyl group of isatins with active site Cysteine.

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Role of Non HLA Genetic Variants in End Stage Renal Disease

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Cytokines and intercellular adhesive molecules (ICAM) play a crucial role in the pathogenesis of primary kidney disease and progression to end stage renal disease (ESRD). Cytokine secretion is reported to be dependent upon the SNP's located in the cytokine genes. The role of different polymorphisms of cytokines and ICAM genes as a probable susceptibility factors for ESRD have been explored in the present study.

The study was conducted on 258 ESRD patients and ethnically matched 569 controls. Individuals were genotyped for *IL-6* (G174C), *IL-4* (C590T), *TNF-α* (-G308A and -G238A) and *ICAM-1* (A469G) gene polymorphisms using standard PCR-RFLP based method.

We observed significant difference in the genotype frequencies of the *TNF-α* -308AA (p=0.001, OR=7.61, 95%CI=2.1-27.9), *TNF-α* -238AA (p=0.001, OR=5.8, 95%CI=2.2–15.1). Further, C allele of *IL-6* -G174C and G allele of *ICAM-1* A469G were significantly different in ESRD patients when compared to controls (p=0.0001; OR=5.5, 95%CI=3.9-7.7 and p<0.0001; OR=3.8, 95%CI=3.1-4.7). For the *IL-4* C590T polymorphism, though the homozygous mutant genotype (TT) was not found to be significantly associated with ESRD, a statistically significant association with T allele (p=0.0001) was found with the ESRD. Further, combined analysis revealed a higher risk in ESRD patients with low *IL-4* and high *IL-6* producing genotypes and high producing genotype of *TNF-α* (308 and 238) with the increased risk of ~6.0 fold and 3.3 fold respectively. Our results suggest that *IL-6, IL-4, TNF-α* and *ICAM* gene polymorphism may be risk factors for ESRD.

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Human Embryonic Stem Cell Based High Throughput Screening Platform: A Biomarkers Based Approach for Predicting Human Developmental Toxicity

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It is becoming increasingly imperative to asses the teratogenecity of new chemical entities (NCEs) and drugs before they enter the market. Ethical limitation inhibit such studies in pregnant women. The current study attempts to create a 3-Dimentional in vitro platform that mimics human peri-implantation embryonic development using embryoid bodies (EBs) derived from human embryonic stem cells (hESCs). A layer of human endometrial cell line (CRL4003) was coated on layers of extracellular matrix proteins eg; fibronectin and collagen on low melting agarose (0.5%), to create a bio-mimetic platform similar to the implantation site. A time course study on EBs was done over a period of 20 days, to understand the induction of germ lineages. The expression profile of the ectoderm, endoderm, mesoderm and trophectoderm lineage markers, such as beta III-tubulin, GATA4, BMP2, Brachury hANP, cTnT, ABCG2, GATA2, BMP4, HAND1 and beta-hCG, were studied, by SQ and QRT-PCR and immunofluorescence. The lineage composition of smooth surfaced EBs (SSEBs) at day-6 closely resembled the human peri-implantation blastocyst. Inhibition in the induction of any of the lineages caused by exposure to a NCE was confirmed by lack of biomarker expression and by loss of the ability of the SSEBs to functionally differentiate into particular lineages. Using proven embryotoxic componds we demonstrated that the model closely mimiced peri-impantation development and was sensitive even at very low doses. This model is adoptable to a 96 well plate format for high through put screening of NCEs.