CO-ORGANIZED EVENT

International Conference on

Toxicology and Clinical Pharmacology

&

2nd International Conference on

Generic Drugs and Biosimilars

December 14-16, 2017 Rome, Italy

Keynote Forum

Day 1

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Manuela Marcoli, Clin Exp Pharmacol 2017, 7:6(Suppl)
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Manuela Marcoli

University of Genova, Italy

Astrocytes and glutamate in striatum: A2A-D2 receptor-receptor interaction controls glutamate release from striatal astrocytic processes

In the 1980s, a new model of chemical signal recognition/decoding was proposed, according to which integrative information handling already occurs at membrane level, via receptor-receptor interactions. Specifically, evidence for striatal A2A and D2 receptor-receptor interaction in A2A-D2 heterodimers in striatal neurons, opened new perspectives on the Parkinson's disease pathophysiology, and provided new targets for anti-parkinsonian drugs. Roles for astrocytes, the most numerous cells in the nervous system, and relevance of the neuron-astrocyte network function in disease vulnerability are increasingly recognized. In particular, astrocyte dysfunction at tripartite synapses and altered glutamatergic transmission are emerging in neuropsychiatric disorders including the Parkinson's disease. Despite the change from a neurocentric to an astrocentric view of neuropsychiatric disorders, and major attention to striatal A2A and D2 receptors, striatal glial A2A and D2 receptors have so far received scarce attention. Our findings suggest - combining confocal microscopy and functional neurochemical approaches on purified preparations of astrocyte processes from adult rat striatum and indicate a crucial integrative role of A2A-D2 circuits at the plasma membrane of striatal astrocyte processes in the control of glutamatergic transmission. Indeed, we obtained evidence that: D2 and A2A receptors are expressed in striatal astrocyte processes; D2 receptors inhibit the release of glutamate from astrocyte processes; astrocytic A2A and D2 receptors can form A2A-D2 heterodimers; homocysteine can reduce D2-mediated control of astrocytic glutamate release. It is to note that hyperhomocysteinemia has been hypothesized to play roles in tardive L-dopa side-effects in Parkinson's patients. Notably, expansion of presynaptic astrocyte processes, and altered neuron-astrocyte interactions at striatal glutamatergic synapses, have been found in Parkinson's disease. Thus, reduced D2-mediated control at striatal presynaptic astrocyte processes might result in an increase in synaptic glutamate level and in turn helps understand how astrocytes (and remodeling of astrocyte processes) contribute to the pathophysiology of Parkinson's disease.

Biography

Manuela Marcoli has completed her MD degree from Pavia University, Italy (PhD. Degree in Clinical Pharmacology from Pavia University, Italy). She is Professor of Pharmacology at the University of Genova, Italy. She has over 85 publications that have been cited over 1300 times, and her publication H-index is 22 and has been serving as a Reviewer of reputed Journals.

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Karen L Houseknecht, Clin Exp Pharmacol 2017, 7:6(Suppl)
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Karen L Houseknecht

University of New England, USA
Maine Medical Center Research Institute, USA

Mechanisms underlying adverse endocrine and metabolic side effects of Atypical Antipsychotic (AA) medications: Central vs. direct effects

Atypical antipsychotic medications (AA) are FDA approved for psychosis associated with schizophrenia, bipolar disorder and irritability associated with autism. AA display complex pharmacology, antagonizing multiple G-protein coupled receptor families. Antagonism of dopamine receptors is thought to be a pivotal component of clinical efficacy. Despite FDA warning labels for metabolic side effects, these are among the most highly prescribed drugs world-wide due to prescribing for non-approved indications. Common clinical side effects include obesity, dyslipidemia, hyperglycemia, sudden cardiac death and increased fractures. Despite the severity of these side effects, there is a paucity of literature examining the underlying pharmacology. We and others have shown that central/indirect side effects of AA include increased appetite and obesity, hyperprolactinemia and hypothalamic insulin resistance, which underlies hepatic insulin resistance. The mechanisms underlying AA-induced dyslipidemia and increased fractures have not been elucidated. Our laboratory is focusing on the emerging side effects of AA medications on bone. Clinical data show that fracture risk is elevated in schizophrenic patients treated with AA vs. the general population, and limited studies show that patients treated with risperidone (RIS) have reduced bone mineral density. We hypothesize that AA impact bone biology by both indirect and direct mechanisms. Our approach includes evaluating effects of clinically relevant doses of AA in pre-clinical models as well as direct effects on bone cells *in vitro*. We explored the role of hypogonadism in RIS-induced bone loss and developed bioanalytical methods to quantify dynamic concentrations of dopamine and RIS in bone marrow to evaluate possible direct drug effects *in vivo*. Our overarching goal is to elucidate the pharmacology associated with undesirable health effects of AA medications to better inform prescribing practices and drug discovery efforts. With such a large patient population taking these medications, these data are of special concern for vulnerable populations including children and the elderly.

Biography

Karen L Houseknecht is currently Professor of Pharmacology, College of Osteopathic Medicine, and Interim Dean of the College of Pharmacy at the University of New England (Portland, Maine USA). She received her PhD from Cornell University and has held multiple leadership positions in academic and corporate research organizations. She is the author of over 50 peer-reviewed publications and her NIH-funded research program focuses on new therapeutic discovery (including drug metabolism) and the pharmacology underlying adverse metabolic effects of psychiatric medications.

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Iben Larsson, Clin Exp Pharmacol 2017, 7:6(Suppl)
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Iben Larsson

Amgros, Denmark

Extractable study for two plast syringes

The extractable profiles for single-use technologies represents an important aspect of pharmaceutical production to minimize any possible compromise in drug product quality or potential risk to patients by identifying substances that may potentially leach from such devices. Approach for the extractable assessment of prefilled syringes is described. Syringes from two different brands were analysed along with their corresponding plunger stoppers. The presented methodology represents a reference point for further studies focused on the characterisation of extractables and leachables from prefilled syringes.

Biography

Iben Larsson, MSc in Polymer Chemistry and PhD in Powder Technology, is employed at Amgros I/S, the Danish Regions' Pharmaceutical organization, in Denmark as Senior Research Scientist. He/She is a Member of the Expert Group, European Paediatric Formulary, in European Directorate for the Quality of Medicines & HealthCare (EDQM) and the Pharmacy Subcommittee under the Danish Pharmacopoeia Commission. He/She has broad experience within the field of stability of cytostatic and biologic drugs together with drug interaction with primary packaging as well as in depth knowledge of micronization of poorly soluble drugs by grinding techniques.

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Christopher Milne, Clin Exp Pharmacol 2017, 7:6(Suppl)
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Christopher Milne

Tufts University, USA

Improving compliance with EMA and FDA pediatric regulations by improving the efficiency of pediatric drug development

While the list of unmet needs in child-appropriate drugs remains long, so does the list of R&D challenges, including recruitment of patients, availability of experienced investigators, high development costs, and increasingly complex regulatory requirements. Prioritization of where to place resources is needed to help pediatric drug devel¬opers comply with regulations and set up frameworks for efficient pediatric drug R&D. In this presentation, we will discuss the hierarchy of clinical trial data and how to ascertain the efficiency of each step and arrive at estimates for the numbers of assessments, exposures, participants, etc. Pediatric drug development typically necessitates accessing dozens of sites in multiple countries just for a single study, which entails managing inevitable logistical issues, both planned and unplanned, while having to complete trials in a short time frame with long term follow-up. Responding to these challenges can be accomplished through a stakeholders' working group of drug developers, patient advocacy organizations, academic partners, and regulatory agencies that can establish priorities and deliv-erables, while enhancing close cooperation and responsive communication. Also critical is the recognition that because of complications ranging from age-based variability in dosage forms to formulation stability, oral dosage forms can be challenging but globally placed pediatric-specific formulation developers are addressing the strong interest in developing alternatives to injectables.

Biography

Christopher Milne joined the Center for the Study of Drug Development at the Tufts University School of Medicine (Tufts CSDD) in 1998 as a Senior Research Fellow and has published over 70 book chapters, white papers, and journal articles. Currently, his research interests include: academic-industry collaborations; disease, demographic and market access factors in the emerging markets; incentive programs for pediatric studies, orphan products, neglected diseases, breakthrough therapies, and medical countermeasures (MCMs); and, tracking the progress of new regulatory and research initiatives such as regulatory science, translational medicine, personalized medicine, and FDA User Fee programs.

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Day 2

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Alan R Gintzler, Clin Exp Pharmacol 2017, 7:6(Suppl)
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Alan R Gintzler

State University of New York Downstate Medical Center, USA

Harnessing endogenous opioids for pain relief: Lessons learned from endomorphin 2

Opioids are the most commonly used and most effective drugs for pain relief. However, tolerance develops to the analgesic effects of opioids, which are also addictive, leading to abuse. Recent research provides insights into utilizing endogenous opioids as an alternative to prescription narcotics. The magnitude of pain relief elicited by the spinal application of an opioid found endogenously, endomorphin 2 (EM2), a highly selective mu-opioid receptor (MOR) agonist, varies across the rat estrous cycle – high in proestrus (when circulating estrogens are elevated) but minimal in diestrus (when circulating estrogens are low). This ebb and flow of spinal EM2 analgesia results from variable levels of spinal glutamate and dynorphin activity, as well as pliable interactions within an oligomer containing estrogen receptor α (ERα), MOR, kappa-opioid receptor, aromatase (aka estrogen synthase) and $mGluR_1$/$mGluR_{2/3}$. During diestrus, ERα activated by spinally synthesized estrogens, acts with $mGluR_1$ to suppress spinal EM2 analgesia. In proestrus there is a disengagement of suppressive aromatase/ERα signaling. This is paralleled by both the differential signaling by $mGluR_1$ (when it is activated by glutamate instead of ERα), and elevated spinal dynorphin-activated kappa-opioid receptors. These aggregate changes in diestrus vs. proestrus function as a switch, preventing or promoting spinal EM2 antinociception. The finding that the analgesic effectiveness (in female rats) of spinally applied EM2 depends on functional interactions among multiple identified oligomerized components provides novel targets for developing pharmacotherapies that harness endogenous EM2, and potentially other endogenous opioids, for pain relief. This would likely reduce the need for prescription opioids, lessening the current epidemic of prescription opioid abuse ravaging society.

Biography

Alan Gintzler has completed his PhD from New York University School of Medicine, USA. He is Distinguished Professor and Director of Research, Department of Obstetrics and Gynecology, State University of New York, Downstate Medical Center, USA. He has over 100 publications that have been cited over 4,000 times and his publication H-index is 38. He has been serving as an Editorial Board Member of many reputed journals.

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Shazib Pervaiz, Clin Exp Pharmacol 2017, 7:6(Suppl)
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Shazib Pervaiz

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National University Cancer Institute - NUHS, Singapore

Redox-dependent targeting of mutant RAS driven cancers

RAS family of GTPases is frequently mutated in human cancers. The current therapeutic strategies to target mutant RAS driven cancers rely mostly on inhibitors that either block the farnesylation/geranylation of RAS or inactivate effectors downstream of activated RAS, such as AKT, MEK and ERK. Despite these endeavors, the clinical outcome of patients harboring mutant RAS expressing cancers remain less than optimal. Our recent work highlights a novel strategy to overcome RAS addiction in human colorectal, pancreatic and non-small cell lung cancer that frequently carry RAS mutations. Exploiting the RAS specific activity of a novel small molecule compound, we provide evidence that hyper-activation of mutant KRAS-and not its inhibition-results in massive redox catastrophe culminating in mitochondrial short circuiting and death execution. We also provide evidence to implicate activation of Akt/PKB, downstream of mutant active KRAS, in triggering oxidative stress and autophagy associated cell death. These data and their potential implications for the design of novel therapeutic strategies to target mutant RAS driven cancers will be discussed.

Recent Publications

1. Wong C H, Iskandar K B, Yadav S K, Hirpara J L, Loh T Pervaiz S (2016) Simultaneous induction of non- canonical autophagy and apoptosis in cancer cells by ROS-dependent ERK and JNK activation. PLoS One. 5(4):e9996.
2. Iskandar K, Rezlan M, Yadav S, Foo Chuan Han J, Sethi G, Qiang Y, Bellot G, Pervaiz S (2016) Synthetic lethality of a novel small molecule against mutant KRAS expressing cancer cells involves Akt dependent ROS production. Antioxid. Redox. Signal. 24(14):781-94.

Biography

Shazib Pervaiz holds a Full Professorship in the Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore. Over the years, he has held various leadership positions at the YLL School of Medicine, such as Vice Dean (Research and Graduate Education) and is a Distinguished Visiting Fellow at the Faculty of Health Sciences, Curtin University, Perth, Australia. He is spearheading a group investigating cellular redox status and its impact on cancer cell fate decisions with an overall objective of identifying novel targets for therapeutic intervention. He has authored more than 145 research papers and book chapters and his research work is highly cited in the field, as indicated by over 12000 citations and an H-index of 52 (by Google Scholar). He has been an invited speaker at several international and regional conferences and is serving on the editorial boards of several international peer-reviewed journals. He was elected to the European Cell Death Organization (ECDO) Academy in 2013. Being a Clinician Scientist, he also has an extensive understanding of working with the healthcare sector as well as with the biotechnology and pharmaceutical industries.

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Fabio Geremia, Clin Exp Pharmacol 2017, 7:6(Suppl)
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Fabio Geremia

CTP System, Akka Technologies Group, Italy

Quality aspects for medical devices, quality system and certification process

Medical devices (MDs) are nowadays more and more important in the healthcare industry and the related processes for worldwide regulation and certification are a topic of great interest. In particular, the need for regulation harmonization between European Countries (European Regulation), as well as worldwide, is very important both for Regulatory Authorities and for the industry world. A typical process for an MD development and industrialization phase is covered, providing some case studies and taking into consideration all steps from design up to start-up of the production phase and process validation. All these activities are necessary for the product certification process. The aspects related to the Quality System, Production, Validation and Quality Control are emphasized, proposing an integrated approach, which combines the GMP and ISO requirements (e.g., ISO 13485 and ISO 14971), following a Quality Risk Management (ICH Q9) and, where applicable, an integrated Pharmaceutical Quality System (ICH Q10) structure.

Biography

Fabio Geremia has completed his graduation in Pharmaceutical Chemistry. He has worked in Italian and multinational pharmaceutical companies, in Quality and Production field. 10 years ago, he has joined CTP System group, the biggest Italian company of pharmaceuticals, healthcare and life science consultancy, now part of the multinational group Akka Technologies, where he is a Senior Consultant and a Qualified Person Auditor and the Technical Responsible for Process and Quality Business Area, Northern Italy. Since many years, he collaborates with the Italian association AFI for medical devices and borderline products, for the preparation of publications and presentations.

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Christopher Milne

Tufts University, USA

Impact of value-based pricing on market access in mature, emerging, and developing economies

Outcomes-based agreements, which ensure that drug companies are paid for actual not potential benefits to patients are another way to better align pricing and coverage of drugs with their value, resulting in so-called value-based pricing (VBP). One in four health plans now have at least one outcomes-based contract with a drug maker, an Avalere Health survey showed. In this presentation, we will examine various factors that impact prospects for implementing such arrangements in mature, emerging, and developing markets such as: pre-existing price structures, legal prohibitions, capacity for measuring outcomes, influence of prescriber resistance, who the payer is (i.e., self-pay vs. universal insurance coverage), etc. Another consideration is that while more countries are using Health Technology Assessments (HTAs) in reimbursement decisions, healthcare payers are increasingly demanding real-world evidence (RWE) of value. Yet another set of considerations are still evolving in importance. For example, only 25 percent of drug company CEOs surveyed say that their company involves patients or advocacy groups in the drug price-setting process, but another 27 percent say they don't involve patients now, but plan to do so in the future.

Biography

Christopher Milne has joined the Center for the Study of Drug Development at the Tufts University School of Medicine (Tufts CSDD) in 1998 as a Senior Research Fellow and has published over 70 book chapters, white papers, and journal articles. Currently, his research interests include: academic-industry collaborations; disease, demographic and market access factors in the emerging markets; incentive programs for pediatric studies, orphan products, neglected diseases, breakthrough therapies, and medical countermeasures (MCMs); and, tracking the progress of new regulatory and research initiatives such as regulatory science, translational medicine, personalized medicine, and FDA User Fee programs.

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