chemistry.org
THE WEBSITE OF THE AMERICAN CHEMICAL SOCIETY

American Chemical Society
234th National Meeting & Exposition
August 19-23, 2007
Boston, MA USA

"*Drug for Ischemia:Treatment of Cerebral Ischemia. Recent Therapeutic Strategies*"

Chair Prof. Roberto Pellicciari

Sunday, August 19th, 2007 - 9:00 AM

Location: BCEC, Room: 210A

Sunday, August 19th, 2007 - 9:00 AM
Location: BCEC, Room: 210A

Symposium title: **'Drug for Ischemia'**

Subtitle: **'Treatment of Cerebral Ischemia. Recent Therapeutic Strategies'**

Sponsored by European Federation for Medicinal Chemistry (EFMC)

Organizer: **Prof. Roberto Pellicciari** (President, EFMC)

09:00 AM **Introductory Remarks**
Roberto Pellicciari (Italy) *Dipartimento di Chimica e Tecnologia del Farmaco, Università degli Studi di Perugia, via del Lliceo 1, 06127 – Perugia (Italy)*

09:15 AM (30+ 5 min) **Recent Approaches to the Treatment of Stroke and Cerebral Ischemia**.
Wayne Childers (USA). *Chemical and Screening Sciences and Neuroscience, Wyeth Research, CN 8000, Princeton, New Jersey 08543-8000, USA*

09:50 AM (30 + 5 min) **JNK signalling pathway after MCAo: neuroprotective effect of JNK inhibitor peptide (D-JNKI1)**
Borsello Tiziana (Italy). *Istituto Mario Negri. Laboratorio di Biologia delle Malattie Neurodegenerative, via Eritrea 6220157, Milano (Italy)*

10:25 AM (30 +5 min) **Design, Synthesis and Neuroprotective Effects of Azulenyl Nitrone Spin Traps in Animal Models of Cerebral Ischemia**
David A. Becker (USA). *Department of Chemistry, Florida International University, Miami, Florida, 33199, USA*

11:00 AM (30 + 5 min) **Design and synthesis of novel SHh agonists: SAR and biological evaluation in a cerebral ischemia model**
Haydar S.N. (USA). *Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, New Jersey 08543-8000, USA*

11:35 AM (30 + 5 min) **Necroptosis Inhibition as a Therapeutic Strategy for Cerebral Ischemia**
Gregory D. Cuny (USA). *Laboratory for Drug Discovery in Neurodegeneration, Harvard Center for Neurodegeneration and Repair, Brigham & Women's Hospital and Harvard Medical School, 65 Landsdowne Street, Cambridge, MA 02139, USA*

MEDI 0 [1110528]: Recent approaches to the treatment of stroke and cerebral ischemia

Wayne E. Childers Jr. and Boyd L. Harrison, Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, childew@wyeth.com

Abstract

Stroke is the second leading cause of death worldwide, with an estimated 5.7 million deaths attributed to this disease in 2005 according to the World Health Organization. In the US alone, approximately 700,000 new and recurrent stroke cases occur each year and the annual cost of caring for the 5.5 million survivors is estimated at over $58 billion. Despite nearly two decades of anti-ischemic research, only one drug, the thrombolytic agent Altepase™, is currently approved for use in acute ischemic stroke. However, the limitations inherent in that agent (relatively short therapeutic window, the need to rule out the presence of hemorrhage and the risk of inducing a life-threatening hemorrhage) emphasize the genuine need for safe, efficacious and widely applicable drugs that possess a wide therapeutic window. In the past, compounds targeting various aspects of the ischemic cascade have demonstrated neuroprotective efficacy in pre-clinical animal models of stroke but have failed in the clinic. However, new mechanistic approaches are emerging that target not only neuroprotection but neuroregeneration as well. This presentation will review some of the more recent approaches and mechanistic targets currently under investigation in the quest for an effective drug to treat this debilitating disease.

MEDI 0 [1084378]: Necroptosis inhibition as a therapeutic strategy for cerebral ischemia

Gregory D Cuny, Laboratory for Drug Discovery in Neurodegeneration, Brigham & Women's Hospital and Harvard Medical School, 65 Landsdowne St, Cambridge, MA 02139, Fax: 617-768-8606, gcuny@rics.bwh.harvard.edu

Abstract

Necrosis represents types of cell death morphologically and mechanistically distinct from apoptosis. It is the prevalent form of acute cell death in many pathologies, including cerebral ischemia. Few attempts, however, have been made to develop therapeutics specifically targeting necrosis because of the conventional notion that it is a non-regulated response to overwhelming stress. This concept is directly challenged by recent studies demonstrating the existence of regulated caspase-independent cell death mechanisms with morphological features resembling necrosis. Previously, one type of necrosis has been described and termed necroptosis. The identification of molecules capable of inhibiting necroptosis will assist in elucidating caspase-independent cell death pathways, their roles in disease patho-physiology and provide lead compounds for therapeutic development. The discovery and optimization of three distinct chemical series of necroptosis inhibitors will be summarized in this presentation. In addition, a current working model of the necroptosis cell death pathway will also be presented.

MEDI 0 [1094366]: JNK signalling pathway after MCAo: neuroprotective effect of JNK inhibitor peptide (D-JNKI1)

Tiziana Borsello, Biol. Neurodeg. Disorders Lab, Istituto di ricerche Farmacologiche "Mario Negri", Via Eritrea 62, Milano ITALY 20157, Italy, Fax: +39 02 3546277, borsello@marionegri.it, and M. Repici, Cellular Biology and Morphology Department, University of Lausanne

Abstract

Activation of c-Jun N-terminal kinase (JNK) occurs in ischemia. The biological action of JNK could be inhibited by the JNK inhibitor peptide (D-JNKI1) that contains TAT-cell entry sequence linked to JBD20 sequence (from JIP1/IB1 scaffold protein), and has been designed to block the interaction between JNK and its targets. We showed strong protection by using D-JNKI1 in two models of middle cerebral artery occlusion: transient occlusion in adult mice and permanent occlusion in 14 days old rats. In the former model, intracerebroventricular administration as late as 6 h post-occlusion reduced the lesion volume by more than 90%, a protection that was maintained for at least 14 days and was accompanied by behavioral sparing. In the latter model, systemic delivery reduced the lesion by 78% at 6 h post-ischemia, and by 49% at 12 h. Protection correlated with prevention of increase in c-Jun activation and caspase-3 activation. Taken together these data suggest that D-JNKI1 is a unique and potent neuroprotective agent. However, comprehensive molecular machinery that modulates this powerful protection remains unclear. To clarify this point, we investigated the JNK molecular cascade activation in cerebral ischemia and the D-JNKI1 effects on this cascade. c-Jun activation starts 3h after ischemia and peaks at 6 h in the ischemic core, while in the penumbra it starts at 1h and peaks at 6h. The 6h JNK activation peak correlates well with that of P-c-jun. D-JNKI1 markedly prevented the increase of P-c-Jun in both core and penumbra and powerfully inhibited caspase-3 activation in the core. These results indicate that targeting the JNK cascade in a very specific way, using the TAT cell-penetrating peptide, offers a promising therapeutic approach for ischemia, raising hopes for human neuroprotection.

MEDI 0 [1094992]: Design and synthesis of novel SHh agonists: SAR and biological evaluation in a cerebral ischemia model

Simon N. Haydar[1], David Albers[2], Shirley brunton[3], Tammy Dellovade[2], Boyd L. Harrison[1], Warren D. Hirst[4], Ronald L. Magolda[1], Menelas Pangalos[4], Peter H. Reinhart[4], Lee L. Rubin[2], and Dane M. Springer[1]. (1) Department of Medicinal Chemistry, Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543, Fax: 732-274-4505, haydars@wyeth.com, (2) Curis Inc, (3) Evotec OAI, (4) Wyeth Research, Discovery Neuroscience

Abstract

The vertebrate protein Sonic Hedgehog (SHh) plays critical roles in embryonic development of the nervous system. In the adult nervous system, hedgehog activators have been shown to promote neuroprotection and regeneration in several models of neural disorders such as stroke, Parkinson's disease and peripheral neuropathy. We have developed small molecule activators of hedgehog signaling. The synthesis and structure activity relationship of these molecules will be discussed. These novel compounds were shown to be efficacious in a model of stroke (rat temporary middle cerebral artery occlusion (tMCAO) and are potential novel therapeutics in the treatment of acute stroke.

MEDI 0 [1105774]: Design, synthesis and neuroprotective effects of azulenyl nitrone spin traps in animal models of cerebral ischemia

David A. Becker, Chemistry and Biochemistry, Florida International University, University Park, Miami, FL 33199, Fax: 305-348-3772, beckerd@fiu.edu

Abstract

Much interest has centered on the potential of nitrone spin traps to counter free radical-mediated damage in biological systems. A large corpus of evidence points to oxidizing radicals as contributors to the pathological consequences of cerebral ischemia. Consideration of such evidence has led to the development of the Mitsubishi drug edaravone, a free radical scavenging agent currently in use to treat stroke victims in Japan. In 2006, notwithstanding encouraging results in animal models, the Renovis/AstraZeneca nitrone NXY-059 failed in late Phase III human ischemic stroke trials. The Ginsberg/Becker groups have been actively investigating the neuroprotective effects of azulenyl nitrones, a novel class of nitrones that have demonstrated promising results in models of cerebral ischemia. The stilbazulenyl nitrone STAZN confers neuroprotection at extremely low doses. Perspectives on the genesis, preparation and efficacy of azulenyl nitrones in animal models of cerebral ischemia will be presented.