Summary

Nikolaus Seiler, Benoit Duranton and Francis Raul

The polyamine oxidase inactivator MDL 72527

Polyamine oxidase is a FAD-dependent amine oxidase, which is constitutively expressed in nearly all tissues of the vertebrate organism. In 1985, N^1,N^4-bis(2,3-butadienyl)-1,4-butanediamine (MDL 72527) was designed as a selective enzyme-activated irreversible inhibitor of polyamine oxidase (EC 1.5.3.11). It inactivates, at micromolar concentration and time-dependently, the enzyme in cells, as well as in all organs of experimental animals, without inhibiting other enzymes of polyamine metabolism. MDL 72527 served during nearly two decades as a unique tool in the elucidation of the physiological roles of polyamine oxidase. The compound has anticancer and contragestational effects, and it improves the anticancer effect of the ornithine decarboxylase inactivator (D,L)-2-(difluoromethyl)ornithine (DFMO). Profound depletion of the polyamine pools of tumour cells and effects on different components of the immune defence system are responsible for the anticancer effects of MDL 72527/DFMO combinations. Recently a direct cytotoxic effect of MDL 72527 at concentrations above those required for polyamine oxidase inactivation was observed. The induction of apoptosis by MDL 72527 was ascribed to its lysosomotropic properties. Therapeutic potentials of the apoptotic effect of MDL 72527 need to be explored. Polyamine oxidase is the last enzyme of the polyamine interconversion pathway that awaits the detailed elucidation of its structure and regulation. MDL 72527 should be useful as a lead in the development of inactivators which are selective for the isoforms of polyamine oxidase. Isozyme-selective inhibitors will give more profound insights into and reveal a diversity of specific functions of polyamine oxidase.

Contents

Key Words: Polyamines, putrescine, spermidine, spermine, polyamine oxidase, metabolism, MDL 72527, enzyme inhibitors, cells, cancer therapy, leukaemia, brain damage.

Summary
Zhi Hong and Craig E. Cameron
Pleiotropic mechanisms of ribavirin antiviral activities

Renewed interest in the mechanism of action of ribavirin results from its synergistic enhancement of interferon therapy and the need to develop more efficacious agents to treat hepatitis C virus infection. Since the discovery of ribavirin over 30 years ago by scientists at ICN Pharmaceuticals, many mechanisms of action for ribavirin have been proposed. These include inhibition of host inosine monophosphate dehydrogenase by ribavirin monophosphate, inhibition of viral capping enzymes, inhibition of viral RNA synthesis by ribavirin triphosphate, lethal mutagenesis of viral RNA genomes resulting from promiscuous incorporation of ribavirin triphosphate by the viral RNA polymerase, and modulation of the host immune responses. In this article, we will briefly review the evidence for these mechanisms, emphasizing recent findings. In addition, we will discuss strategies for development of nucleoside analogs that may replace ribavirin in the future.

Contents

Key Words: Ribavirin, levovirin, viramidine, prodrug, deamination, antiviral therapy, nucleoside analog, RNA-dependent RNA polymerase, inosine monophosphate dehydrogenase, RNA virus, mutagen, lethal mutagenesis, quasispecies, error catastrophe, immunomodulation, poliovirus, GB virus B, hepatitis C virus.

Summary
Jie Hong Hu and Charles Krieger
Protein phosphorylation networks in motor neuron death

The disorder amyotrophic lateral sclerosis (ALS) is characterized by the death of specific groups of neurons, especially motor neurons, which innervate skeletal muscle, and neurons connecting the cerebral cortex with motor neurons, such as corticospinal tract neurons. There have been numerous attempts to elucidate why there is selective involvement of motor neurons in ALS. Recent observations have demonstrated altered activities and protein levels of diverse kinases in the brain and spinal cord of transgenic mice that overexpress a mutant superoxide dismutase (mSOD) gene that is found in patients with the familial form of ALS, as well as in patients who have died with ALS. These results suggest that the alteration of protein phosphorylation may be involved in the pathogenesis of ALS. The changes in protein kinase and phosphatase expression and activity can affect the activation of important neuronal neurotransmitter receptors such as NMDA receptors or other signaling proteins and can trigger, or modify, the process producing neuronal loss in ALS. These various kinases, phosphatases and signaling proteins are involved in many signaling pathways; however, they have close interactions with each other. Therefore, an understanding of the role of protein kinases and protein phosphatases and the molecular organization of protein phosphorylation networks are useful to determine the mechanisms of selective motor neuron death.

Contents

Key Words: Amyotrophic lateral sclerosis, motor neuron, NMDA receptor, neurotoxicity, PSD-95, protein kinase, protein phosphatase, protein phosphorylation.

Summary
James O. Schenk
The functioning neuronal transporter for dopamine: Kinetic mechanisms and effects of amphetamines, cocaine and methylphenidate

The dopamine transporter (DAT) is a transmembrane spanning protein that catalyzes the transport of dopamine across the neuronal membrane to concentrate the neurotransmitter inside the cell. Although the uptake of dopamine has been studied since the 1960s, more recent advances in knowledge of the protein itself and in making kinetically resolved measurements of its action have led to more insights into its mechanism and pharmacology. The literature of the kinetics of transporters and kinetic measurements of DAT activity is reviewed to provide an overview of the multisubstrate mechanism of DAT activity, its pharmacology with regard to amphetamine, cocaine and methylphenidate, and correlations of DAT activity with some behavioral outputs.

Contents

Key Words: Amphetamine, benztropine, cocaethylene, cocaine, cocaine self-administration, dopamine, dopamine transporter, fotating disk electrode voltammetry, GBR-12909, locomotor activity, mazindol, methylphenidate, nomifensine, transporter kinetics, *m*-tyramine.

Summary
Laszlo Prokai
Central nervous system effects of thyrotropin-releasing hormone and its analogues: opportunities and perspectives for drug discovery and development

Besides its well-known endocrine role in the thyroid system, thyrotropin-releasing hormone (L-pyroglutamyl-L-histidyl-L-prolinamide) has been long recognized as a modulatory neuropeptide. After a brief overview of the extrahypothalamic and receptor distribution, and of the neurophysiological, neuropharmacological and neurochemical effects of this tripeptide, this review discusses efforts devoted to enhance therapeutically beneficial central nervous system effects via structural modifications of the endogenous peptide. An enormous array of maladies affecting the brain and the spinal cord has been a potential target for therapeutic interventions involving agents derived from thyrotropin-releasing hormone as a molecular lead. Successful development of several centrally active analogues and recent accounts of efforts aimed at improving metabolic stability, selectivity and bioavailability are highlighted.

Contents

Key Words: Thyrotropin-releasing hormone, analogue, mimetic, prodrug, central nervous system, receptor, pharmacology, neurochemistry, metabolism, drug development, neurological diseases.

Summary
David F. Horrobin
A new category of psychotropic drugs: neuroactive lipids as exemplified by ethyl eicosapentaenoate (E-E)

New treatments for psychiatric disorders are urgently required. Recent reviews show that there have been no improvements in efficacy of drugs for either affective disorders or schizophrenia since the first compounds were introduced over 40 years ago. Neuroactive lipids represent an entirely novel class of psychotropic compounds. Ethyl eicosapentaenoate is the first example of this group. Placebo-controlled studies have found it to be effective in depression, in treatment-unresponsive schizophrenia and in tardive dyskinesia. It is extremely well tolerated with none of the usual side-effects of either antidepressants or neuroleptics. It probably works by modulating post-receptor signal transduction processes.

Contents

Key Words: Depression, schizophrenia, bipolar disorder, tardive dyskinesia, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), typical neuroleptics, atypical neuroleptics, clozapine, ethyl eicosapentaenoate (E-E), eicosapentaenoic acid (EPA), arachidonic acid (AA), docosahexaenoic acid (DHA), signal transduction, phospholipids, phospholipases, Huntington's disease.

Summary
Suprabhat Ray, Reema Rastogi and Atul Kumar
Current status of estrogen receptors

Increasing knowledge on structure and function of estrogen receptors is providing information on mechanism of action of estrogen agonists as well as antagonists and in understanding their tissue selective action. However, there are still many factors associated with estrogen response which are poorly understood. Therefore, the task of designing a tissue selective estrogen for use as a pharmaceutical in estrogen dependent disorders, remains an uncertain game. This review provides information on the current status of estrogen receptors for a better understanding.

Contents

Key Words: Estrogen receptors, selective estrogen receptor modulators, estrogen antagonists, hormone receptors.

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