Summary
Fleur L. Strand
Neuropeptides: general characteristics and neuropharmaceutical potential in treating CNS disorders

The general characteristics of neuropeptides are discussed as a background for the understanding of their role in regulation of physiological systems. The extent of those systems that are crucially affected by neuropeptides is vast and the complexity of their interactions makes the clinical focus on a specific neuropeptide unsatisfactory. The clinical potential of neuropeptides affecting eating disorders, CNS behavioral disorders and the neuroregenerative and neuroprotective action of neuropeptides is discussed. It is probable that successful neuropeptide therapeutics will depend upon the application of translational and combinational research using various ingenious combinations of neuropeptides, their agonists and antagonists, neuropeptide receptor agonists and antagonists, improved methods of delivery and the development of peptides targeted to the genetic profile of individual patients.

Contents

Key Words: Neuropeptide characteristics, distribution in CNS, energy homeostasis, neuropeptides and appetite regulation, CNS disorders, inflammation, neuroregeneration, neuroprotection, translational and combinational research.

Summary
David J. Begley and Milton W. Brightman
Structural and functional aspects of the blood-brain barrier

In this chapter the current understanding of the blood-brain and blood-cerebrospinal barriers is reviewed. The development of new and powerful molecular biological techniques, coupled with rapid advances in more traditional structural and physiological studies, have greatly increased our appreciation of the function of the barriers of the CNS. These barriers are now recognised as being reactive and adaptive cell biological, metabolic and transport interfaces rather than simple physical barriers to solute movement.

Contents

Key Words: ABC transporters, blood-brain barrier, blood-CSF barrier, cerebrospinal fluid, choroid plexus, endocytosis, endothelium, epithelium, exocytosis, interstitial fluid, solute transporters, tight junctions, transport.

Summary
Abba J. Kastin and Weihong Pan
Peptide transport across the blood-brain barrier

Understanding the mechanisms of how peptides interact with the BBB is our major approach toward revealing how the brain communicates with the rest of the body. Peptides in the periphery may act on the brain microvessel endothelial cells by binding to cell surface receptors or by transcytosis with subsequent actions on brain parenchyma. Pharmacokinetic studies involving radioactive tracers have proved that intact peptides cross the BBB.

Quantification of passage shows that peptides may gain access to CNS tissue by simple diffusion or by saturable transport systems at the BBB.

Contents

Key Words: Blood-brain barrier, peptides, feeding.

Summary

Richard Grondin, Zhiming Zhang, Yi Ai, Don M. Gash and Greg A. Gerhardt
Intracranial delivery of proteins and peptides as a therapy for neurodegenerative diseases

Parkinson's disease is characterized by a progressive degeneration of the substantia nigra pars compacta dopamine neurons that innervate the striatum. Unlike current treatments for PD, GDNF administration could potentially slow or halt the continued degeneration of nigral dopaminergic neurons. GDNF does not cross the blood-brain barrier and needs to be administered directly into the brain. Due to the progressive nature of PD, sustained delivery of trophic factors may be necessary for optimal, long-term neuronal effects. Novel methods for sustained delivery of GDNF into the nigrostriatal pathway are currently being studied in non-human primates, including computer-controlled infusion pumps. Using this approach, we have demonstrated that chronic infusions of nominally 7.5 or 22.5 μg/day GDNF into the lateral ventricle, the putamen or the substantia nigra, using programmable pumps, promotes restoration of the nigrostriatal dopaminergic system and significantly improves motor functions in MPTP-lesioned rhesus monkeys with neural deficits modeling the terminal stages of PD and in aged rhesus monkeys modeling the early stages of PD. Based on the promising studies of the chronic effects of GDNF in non-human primate models of PD, a pilot study was recently conducted in England on five advanced PD patients. Chronic GDNF infusion into the dorsal putamen, via programmable pumps, resulted in improved motor function in all patients and limited side effects were observed. However, while the data from this intraparenchymal clinical trial in humans look encouraging, extensive blinded efficacy trials will need to be

conducted before it can be determined if chronic treatment with GDNF or other trophic molecules will prove useful in treating patients with PD.

Contents

Key Words: Parkinson's disease, aging, glial cell line-derived neurotrophic factor, rhesus monkey, substantia nigra, putamen, lateral ventricle, programmable pumps.

Summary

David Fortin

Altering the properties of the blood-brain barrier: disruption and permeabilization

The blood-brain barrier, by way of its anatomic and physiologic properties, represents a formidable obstacle to the delivery of therapeutic molecules through the CNS. It is one of the reasons explaining the lack of results obtained thus far in the treatment of CNS pathologies. This chapter discusses strategies designed to bypass the blood-brain barrier, and focuses essentially on one of these approaches, the osmotic blood-brain barrier disruption technique. After a brief introduction to the history and genesis of the procedure, new insights in pre-clinical studies supporting the osmotic blood-brain barrier disruption are detailed. The transition from the laboratory to the clinic is explained, and clinical application of the procedure is detailed, with emphasis on malignant brain tumor treatment.

Contents

Key Words: Blood-brain barrier, brain tumor, disruption, osmotic opening, permeabilization.

Summary
Katalin Prokai-Tatrai and Laszlo Prokai
Modifying peptide properties by prodrug design for enhanced transport into the CNS

The prodrug design is perhaps the most versatile chemical manipulation strategy that attempts to solve or reduce certain identifiable shortcomings (e.g., insufficient solubility, limited tissue-uptake, etc.) of a drug. This technique relies on bioreversible chemical alteration of the target agents to produce their prodrugs with improved physicochemical characteristics compared to those of the parent drugs. For peptides displaying activity in the central nervous system (CNS) such as enkephalins, thyrotropin-releasing hormone, etc., the transient chemical modification(s) leading to their prodrugs may be a very challenging task for medicinal chemists. Peptide prodrug design usually aims at achieving lipophilicity and improved metabolic stability, thus enabling a better penetration and transport across the blood-brain barrier; however, the outcome of the prodrug approach is often unpredictable. Several criteria have to be fulfilled to create useful, CNS-permeable prodrugs for peptides. A critical issue in the design of prodrugs for CNS-active peptides is the choice and precise placement of the cleavable moiety or moieties to obtain efficacious absorption, distribution, metabolism and an optimal pharmacokinetic/pharmacodynamic profile. No uniform method has been possible for true CNS-targeting of all CNS-active peptides with potential clinical usefulness due to the complex structure of peptides/proteins and the intricate interplay among factors governing the entry and retention of these biomolecules in the CNS. Nevertheless, progress in this area has been steady and the continued exploration and development of the prodrug strategy for peptides reviewed in this chapter are clearly warranted.

Contents

Key Words: CNS-targeting, enkephalins, passive transport, prodrug, prodrug-amenable peptide analogue, thyrotropin-releasing hormone.

Summary

Suresh P. Vyas

CNS-delivery via conjugation to biological carriers: physiological-based approaches

The blood-brain barrier (BBB) is an insurmountable barrier for a large number of bioactive compounds. Several transport systems for nutrients and endogenous biologicals exist and operate in the brain capillary endothelial cells, constituting an integral part of the BBB. Differences in the affinity and the maximal transport activity among these transport systems can be used selectively for the design of strategies to control or retard delivery of drugs into the brain. Physiologically based strategies essentially utilize intrinsic transport mechanisms associated with the BBB, which specifically operate for macromolecules. These strategies include use of pseudonutrients, cationic antibodies and chimeric peptides for delivery of drugs to central nervous system (CNS). Pseudonutrients are polar micromolecular drugs that have a molecular structure mimicking a nutrient that normally permeates following carrier-mediated transport, whereas cationic antibodies follow absorptive-mediated transcytosis through the BBB. The most widely utilized approach for brain drug delivery is chimeric peptide technology. In addition to vector-mediated transport, engineered colloidal carrier systems, viz., surface modified liposomes and nanoparticles have also been investigated for brain delivery. In essence, physiologically based approaches offer potentials for bioactive delivery to the CNS using safe biomodules categorically functional at biophysiological level.

Contents

Key Words: Blood brain barrier; cationized antibodies, chimeric peptide; central nervous system; drug delivery; liposomes; nanoparticles; peptide nucleic acid.

Summary
Jamal Temsamani and Jean-Michel Scherrmann
Peptide vectors as drug carriers

Despite major advances in neuroscience, many potential therapeutic agents are denied access to the central nervous system because of the existence of the blood-brain barrier. The current challenge is to develop drug delivery strategies that will allow the passage of therapeutic drugs through the blood-brain barrier in a safe and effective manner. To overcome this problem, a strategy has been developed which consists of conjugating the molecule of interest to cell-penetrating peptides that are efficiently transported across the cell membranes. SynB peptide vectors have shown the ability to deliver various molecules, such as doxorubicin, benzyl-penicillin, dalargin and streptavidin, across the blood-brain barrier in a safe and effective manner. This enhancement in brain uptake resulted also in an enhancement of pharmacological activity. These results support the usefulness of a peptide-mediated strategy for improving the availability and efficacy of central nervous system drugs.

Contents

Key Words: Peptide-vector; drug delivery; central nervous system; blood-brain-barrier; multidrug resistance.

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