

DRUG TARGETING TO THE NERVOUS SYSTEM BY NANOPARTICLES

This application is a continuation of Ser. No. 08/556,125 filed on Nov. 9, 1995 now abandoned, which is a continuation of Ser. No. 08/203,326 filed Feb. 28, 1994 now abandoned.

FIELD OF THE INVENTION

This invention relates to both a novel and useful method of targeting and delivering drugs and diagnostics to the brain and a drug targeting system itself. More particularly, the invention pertains to a nanosphere drug targeting system which allows any drug ("drug as used herein includes any substance given for therapeutic and/or diagnostic purposes) to cross the blood-brain barrier (bbb) to achieve one or more of the following benefits: reducing the dose of a drug or diagnostic given peripherally, allowing drugs that normally do not cross the bbb to penetrate into the brain, and reducing the peripheral side effects by improving the relative amount of the drug reaching the brain.

BACKGROUND OF THE INVENTION

General Pharmacology Principles of BBB

The treatment of nervous system disorders can be achieved by giving drugs which affect nervous system function or dysfunction in animals or patients. Typically, such drugs are given by peripheral application, either via the oral or the systemic route. While many drugs are able to cross the bbb, others do not pass the bbb efficiently or not at all and are only effective when given directly into the brain. The term "blood-brain barrier" or "bbb", as used herein, refers to the bbb proper as well as to the blood-spinal barrier. The blood-brain barrier, which consists of the endothelium of the brain vessels, the basal membrane and neuroglial cells, acts to limit penetration of substances into the brain. Sometimes the structure of the bbb is subdivided into two components: the endothelial or capillary barrier and the ependymal barrier Banks, W. A., Kastin, A. J., Barrera, "Delivering peptides to the central nervous system: Dilemmas and strategies," *Pharm. Res.* 8:1345-1350(1991). The nature of the substance penetration through the bbb has not yet been determined but it is known that many of the regulators of brain function such as cytokines, transferrin, encephalins and endorphines can pass through the bbb from the blood vessels into the brain Raeissi, S., Audus, J., "In vitro characterization of blood-brain barrier permeability to delta sleep-inducing peptide." *J. Pharm. Phys.* 41:848-852 (1989); Zlokovich, B., Susie, V. T., Davson, H. Begley, D. J., Jankov, R. M., Mitrivic, B. M., Lipovac, M. N., "Saturable mechanism for delta sleep-inducing peptide (DSIP) at the blood-brain barrier of the vascularly perfused guinea pig brain." *Peptides* 10:249-254(1989); and Zlokovich, B., "In vivo approaches for studying peptide interaction at the blood-brain barrier." *J. Control. Rel.* 13:185-201(1990). However, many substances which can affect the Central Nervous System (or CNS) such as adenosine, β -endorphin, synthetic analogs of endogenous peptides Houghten, R. A. Swann, R. W., Li, C. H., " β -Endorphin: Stability, clearance behaviour and entry into the central nervous system after intravenous injection of the tritiated peptide in rats and rabbits." *Proc. Natl. Acad. Sci. USA* 77:4588-4591(1980); Levin, E. R., Frank, H. J. K., Weber, M. A., Ismail, M., Mills M., "Studies on penetration of the blood-brain barrier by atrial natriuretic factor." *Biochem. Biophys. Res. Commun.* 147:1226-1231(1987) Sakane, T., Tanaka, C., Yamamoto, A., Hashida, M., Sesaki, H., Ueda, H., Takagi, H., "The

effect of polysorbate 80 on brain uptake and analgesic effect of D-kyoto." *Int. J. Pharm.* 57:77-83(1989), as well as some excitatory and inhibitor amino acids and trophic factors, penetrate poorly or not at all through the bbb. At present, drugs with no bbb penetration or poor bbb penetration can only be given by direct CNS infusion or by implantation of controlled-release polymers. (See, e.g., U.S. Pat. No. 4,883, 666, Sabel et al.) Thus, many potentially potent drugs are not useful clinically due to their inability to pass the bbb.

In addition, many drugs exist today which affect the brain in a desirable manner but cannot be used because they have severe side effects because they affect peripheral organs of the body and/or the peripheral nervous system. Because of this there is a long-felt need to reduce the side effects of drugs directed to the CNS while reducing the drugs' activity in peripheral organs and increasing the action in the nervous system.

Overcoming the BBB by Difference Approaches

One way to overcome these limitations of traditional drug therapy is to increase the relative amount of drug which passes the bbb. The reasoning is that if one can increase the amount of the drug crossing the bbb while reducing the peripheral dose of a given drug or diagnostic substance, the peripheral side effects of the drug are also less severe, while at the same time maintaining the desired effect in the brain.

A number of approaches have been described in the prior art to increase drug penetration through the bbb.

One approach has been to alter the function of the bbb itself. For instance, osmotic agents, when given peripherally (such as by intravenous injection), result in the opening of the bbb. Further, some drugs acting on the CNS can change the permeability of the bbb for other substances; cholino-mimetic arecolines, for instance, have been reported to induce changes of drug penetration through the bbb Saija, A., Princi, P., De Pasquale, R., Costa, G., "Arecoline but not haloperidol produces changes in the permeability of the blood-brain barrier in the rat." *J. Pharm. Pha.* 42:135-138 (1990).

Other drugs which can be given to alter the permeability of the bbb are disclosed in U.S. Pat. Nos. 5,059,415 and 5,124,146, both issued to E. A. Neuwelt. Bradykinin is one specific drug with such effects. (U.S. Pat. No. 5,112,596, issued to Malfroy-Camine). Another method comprises giving permeabilizer peptides such as A-7 or conformational analogs thereof. (WO 92/18529, an application of J. W. Kozarich et al.). A relatively invasive method has been proposed by A. Tomasz and E. Tuomanen (WO 91/16064) who give parenteral injections of purified cell wall or cell wall fragments of eubacteria such as *Streptococcus pneumoniae* to open the bbb.

U.S. Pat. No. 5,260,210 issued to L. L. Rubin et al., discloses a method whereby the permeability of the blood-brain barrier is increased by giving an agent which reduces or interferes with cyclic AMP concentrations or which increases cyclic GMP concentrations.

Any method of changing the permeability of the bbb itself, however, is compromised by the fact that unwanted molecules which the brain is normally protected from by the bbb can pass the bbb as well and exert undesirable side effect. Further, such an effect is non-specific so these methods are impractical due to unpredictable and uncontrollable consequences to the nervous tissue.

Another approach is the modification of the drug molecules themselves. For instance, macromolecules, such as proteins, do not pass the bbb at all. For example, one can first isolate the macromolecule active site, i.e., the portion of the molecule which triggers the biologically desirable event,