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New Directions in CNS Drug Delivery

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This commentary expands on the above article in 2 ways. First, it provides more recent information on polymer-based drug delivery systems. Second, it discusses experimental systems that may be clinically viable in the future such as prodrugs, cell-polymer transplants and gene transplants.

WE found the article by Robert Harbaugh informative and believe it provides a useful review of several CNS drug delivery systems. Our goal in writing this commentary is to expand on two areas in this article. First, we will provide more up-to-date information and a broader perspective on the use of polymer-based drug delivery systems. In addition, we will suggest other systems that are in an experimental stage, but which may significantly impact drug delivery treatments for brain disease in the future.

POLYMER-BASED DELIVERY SYSTEMS

Polymer-based delivery systems such as nitroglycerin skin patches or injectable polymeric microspheres are rapidly being utilized in many diseases because of their convenience, low cost compared to all other methods of drug delivery discussed in the Harbaugh article, ease of implantation, and ability to protect biochemically unstable compounds. With respect to the brain, animal studies over the past few years have already shown successful controlled release of dopamine (7), bethanechol (10), dexamethasone (21), and anticancer agents (5, 18–20, 25) for prolonged time periods. In addition, the application of polymer-based drug delivery systems in neurological disease has rapidly expanded within the past few years. In 1987, a Phase I–II five-center clinical trial using a bioerodible polymer releasing the drug BCNU (Carmustine) for brain tumor patients was initiated (3,6). Twenty-one patients were implanted with a polyanhydride polymer containing BCNU. No detectable toxicity from the polymer implants was noted. Based on these results, a 16-center multi-institutional Phase III clinical trial for patients with brain tumors is underway. This study is a prospective, randomized, placebo-controlled investigation designed to determine the effectiveness of biodegradable polymers in releasing chemotherapeutic agents for recurrent malignant brain tumors.

Dr. Harbaugh mentions that there are considerable potential disadvantages associated with the use of polymer delivery systems. Two such disadvantages mentioned were 1) that only one compound can be evaluated and 2) that dose adjustment will not be possible once the polymer is implanted. We do not agree with either of these comments. First, it is easy to place multiple compounds into any polymer system and release them at a controlled rate (16). There is simply no reason why polymers are any more limited in this respect than pumps or any other drug delivery vehicle. Second, with respect to dose adjustment, ongoing research has already shown that there are several techniques capable of regulating release from polymeric delivery systems. For example, polymer implants have been designed that contain both magnetic beads and the drug; with the application of an oscillating external magnetic field, the drug can be released at rates up to thirty times its basal value (8). In addition, ultrasound has been shown to greatly enhance both the degradation rates of biodegradable polymers and the release rates of incorporated drugs in such polymers (11). Such approaches have already been used to successfully regulate insulin release from polymer matrices in experimental animals (12). While these externally regulated systems have not yet been applied to the CNS, appropriate triggering devices could be developed to control the release of drugs from polymer matrices implanted in the brain. Polymer systems have also been designed so that direct feedback can be provided by the incorporation of enzymes or antibodies in the polymers leading to "intelligent" polymer delivery systems (9).

Furthermore, Dr. Harbaugh mentions that for very long-term delivery it may be necessary to repeat the implantation procedure, but it should be noted that the polyanhydride systems already in clinical use for brain tumor patients have been designed so that the drug can be released for approximately three weeks (3,6). With minor chemical modifications, these and other polymers can release biologically active drugs for up to five years (14,17). In fact, an advantage of the polymers is their ability to "protect" biochemically unstable drugs from degradation (5). The need to repeat implantation is dependent both on the therapy and on the level of the drug required.

Another advantage of the polymer delivery system to the brain is the ease of changing configurations in accordance with the specific need. For example, in our study of recurrent brain tumors, the chemotherapeutic agents are incorporated into polymers that are shaped like discs which are placed against the brain tumor interface surface. The same polymer can be made into a mesh, a cylinder, or a rod. In addition, there is minimal risk of infection because the polymers are biocompatible and biodegradable. Currently under development are microspheres (15) which can be delivered with super-selective angiographic techniques allowing for precise targeting to different regions of the brain. Microspheres may also be injected stereotaxically, which is a simple surgical procedure.

OTHER ALTERNATIVE DRUG DELIVERY SYSTEMS

In addition to the systems mentioned in Dr. Harbaugh's article that are now in clinical trials such as pumps, neurotransplants and polymers, there are a variety of experimental systems under study in animal models. These include prodrugs, cell-polymer transplants, and gene transplants.

There have been a variety of interesting prodrug approaches to deliver drugs to the brain. The idea of a prodrug is that a drug, normally unable to cross the blood-brain barrier, is complexed to an agent that enables it to penetrate the blood-brain barrier. There have been several approaches to achieve this goal. For example, Pardridge and colleagues have coupled cationized albumin to β-endorphin (13) and have altered the charge of immunoglobulins (22) to significantly enhance the transport of these molecules in isolated bovine brain microvessels. Bodor and co-workers have linked biologically active agents to a lipoidal hydropyridine carrier that penetrates the blood-brain barrier. Once penetration has occurred, the carrier oxidizes to its ionic pyridium salt preventing its elimination from the brain (2). Similarly, Burch *et al.* have reported that linking CCNU-OH to a reduced chemical delivery system results in selectively enhanced delivery in the rat brain (4).

Other interesting approaches for delivering agents involve cell transplantation techniques. Aebisher *et al.* have recently encapsulated neural cells in polymer fibers and placed them in the brain. By implanting neurotransmitter-secreting cells that have been encapsulated inside a polymer, one has a viable source of neurotransmitter, while at the same time immune rejection is minimized (1). Another possible approach would be to implant polymers that release growth factors or other agents in conjunction with neural transplants to potentially improve the efficacy and/or viability of the neural transplants. Similarly, the "intelligent" feedback systems, as described above, that release necessary substances "on demand" or in a given temporal sequence could be implanted with neural transplants to affect specific aspects of a transplant's growth. For example, one could design a system that releases factors that might first enhance neuronal elongation and then would subsequently release another factor more effective in enhancing synaptogenesis.

The use of vectors and genes transplanted directly into the brain or as a method for developing new types of transplantable cells are also potentially important methods of CNS delivery. For example, rat fibroblasts, infected with a retroviral vector carrying the rat gene for tyrosine hydroxylase (TH) (a synthetic enzyme for catecholamines, which converts tyrosine into L-DOPA) have been transplanted into the brains of rats with unilateral 6-hydroxydopamine lesions, a rodent model of Parkinson's disease. After transplantation, TH was expressed in these cells in the brain (24). In addition, it may also be possible to use similar methods involving transfecting specific brain cells with vectors in vivo in order to impart new functions to these cells as has been successfully achieved in certain animal models for liver cells (23).

In summary, the paper by Harbaugh provides a useful perspective of systems that are currently being used clinically. However, the rapid pace at which technology is developing both in polymer chemistry and in molecular and cell biology should not be overlooked in viewing how drug delivery to the brain may change. While still experimental, these new approaches may significantly affect the way drugs are delivered in the future. Furthermore, some of these approaches will ultimately lower the cost of CNS drug delivery and many are implemented more easily than surgically implantable pumps. We believe the polymer-based systems are particularly attractive for surgical implants and the rapid rate at which biodegradable polymers are being developed and successfully implemented for other clinical uses, will enable them to play a major role in CNS drug delivery.

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Delivery of Neuroactive Compounds to the Brain: Potential Utility of Genetically Modified Cells

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Several methods for chronic delivery of compounds to the central nervous system (CNS) now exist. Peripheral drug administration is generally safest, but not always effective. If direct CNS delivery of a substance is required, then CNS implantation of drug-delivery systems or grafting of various cell types to the brain can be performed, although none of these interventions are yet of consistent, proven benefit in Alzheimer's disease and other neurodegenerative disorders. Grafting of genetically modified cells to the brain may be an alternative delivery system of some substances to the CNS.

"Healing is a matter of time, but it is sometimes also a matter of opportunity." (Hippocrates)

CENTRAL administration of neuroactive compounds may be necessary when, as pointed out by Dr. Harbaugh, peripheral administration suffers from erratic drug absorption, excessive protein binding, peripheral drug metabolism, adverse systemic effects, and poor blood-brain barrier penetration. Poor patient compliance is not, of course, alone a sufficient reason to resort to central drug administration, but may be an ancillary advantage to central administration. Since central administration of compounds entails risks not present with peripheral administration, all possibilities for peripheral administration should be exhausted before resorting to a central approach. For example, in the case of dopamine replacement therapy in Parkinson's disease, dopamine does not cross the blood-brain barrier (BBB), but its metabolic precursor, L-DOPA, does. Problems with peripheral metabolism of L-DOPA are minimized by the co-administration of a peripheral decarboxylase inhibitor, carbidopa. In the case of compounds such as NGF, problems with BBB penetration and/or protein binding might be overcome by binding NGF to lipid carriers [for review see (2)]. Thus, modifications of neuroactive compounds or co-administration of modifying agents may, in some cases, result in efficacious and safe delivery of compounds to the CNS.

When central drug delivery is required, the methods presented in the accompanying review are available. Chronically implanted hardware in the brains of humans can function successfully for decades, as demonstrated in patients with ventriculoperitoneal shunts or ventriculoatrial shunts, which drain excess cerebrospinal fluid from the brain. While the latter devices do not involve the use of an active pump, they do demonstrate that the human CNS tolerates chronic cannulation. The only major problems encountered with these systems involve occasional occlusion of shunt tubing or infection, problems which might also occur with chronic CNS infusions. Work with chronic CNS infusions in animal models has demonstrated occasional problems with parenchymal necrosis around central infusion sites, which appears to depend upon the flow rate of the pump (7). Inadvertent parenchymal damage as well as infections have also been observed in humans receiving intracerebroventricular infusions of chemotherapeutic drugs (3, 4, 6). Thus, the nature of the substance being infused and its rate of flow may affect tolerance to central infusions.

Hardware problems can be avoided by grafting cells to the CNS that either secrete a desired substance, or that restore a lost function directly. Success with this approach in animal models of Alzheimer's disease, Parkinson's disease, and endocrine deficiency demonstrate the realistic potential of fetal grafting in the treatment of human disease. However, when human fetal cells are used as donors, issues related to optimal donor cell age, donor cell availability, graft rejection, and ethics must be addressed. The ideal donor cell for grafting to the human CNS would be readily available, survive well, incite no immune response, secrete a desired substance in adequate quantities for extended periods, and pose no ethical problems. The genetic modification of cells for neural transplantation may offer promise in all these respects.

We have been investigating the use of genetically modified fibroblasts, since these cells are easily obtained and manipulated in vitro, and survive transplantation to the rat CNS for at least several months (1). Fibroblasts genetically modified to produce NGF have been used to prevent cell loss in vivo in a rat model of cholinergic

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