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Distribution of drugs following controlled delivery to the brain interstitium

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Abstract

Intracranial controlled release polymers have been used for drug delivery to the brain, bypassing the blood brain barrier (BBB). By understanding the rates and patterns of transport in the local tissues, it is possible to design delivery systems that provide the optimal spatial and temporal pattern of chemotherapy within the intracranial space. This paper reviews the kinetics of drug release from polymeric controlled release implants, and describes the fate of drug molecules following release into the brain interstitium. Potential improvements in drug delivery based on the understanding of the mechanisms of drug release, transport and elimination are discussed.

Introduction

Systemic delivery of drugs to treat tumors and neurological disorders in the central nervous system has been difficult due to the blood-brain barrier (BBB), which has low permeability to hydrophilic drugs and macromolecules. Several approaches have been proposed to bypass the BBB. Chemical approaches include facilitated transport of drugs through the BBB by conjugating the drug to anti-transferrin receptor [1] or by increasing the lipophilicity of the drug. Other approaches include transient osmotic disruption of the BBB [2], microinjection [3], continuous infusion with osmotic pumps [4], high-flow microinfusion [5], and controlled release from polymeric implants (see Table 1). These methods share the advantages of higher organ specificity, lower systemic toxicity, lower serum protein binding and lower peripheral drug inactivation when compared to systemic administration. Among these approaches, only controlled release systems and infusion provide sustained drug delivery. Controlled release systems, in particular, do not require intervention after the polymer is implanted. In addition, polymer implants protect unreleased drug from degradation in the body, and permit localization of extremely high doses (up to the solubility of the drug) at precisely defined locations in the brain.

Bypassing the BBB, however, is not sufficient for effective drug delivery. Consider a polymer implant within the brain tissue, which provides a prolonged release of chemotherapy drug into the extracellular space of the brain (Fig. 1). Drug molecules released into the interstitial fluid must penetrate into the brain tissue to reach tumor cells distant from the polymer. Before these drug molecules reach the target site, they might be eliminated from the brain interstitium by partitioning into brain capillaries or cells, entering the cerebrospinal fluid, or being inactivated by extracellular enzymes. Regardless of the delivery system chosen, one must understand the dynamics of local transport and elimination in the brain tissue, since these factors determine the likelihood that the drug can reach the target site at therapeutic concentrations. This review describes the kinetics of drug release from polymeric controlled release implants, presents mathematical models for describing the fate of drug molecules following release into the brain interstitium, and discusses the optimal charac-

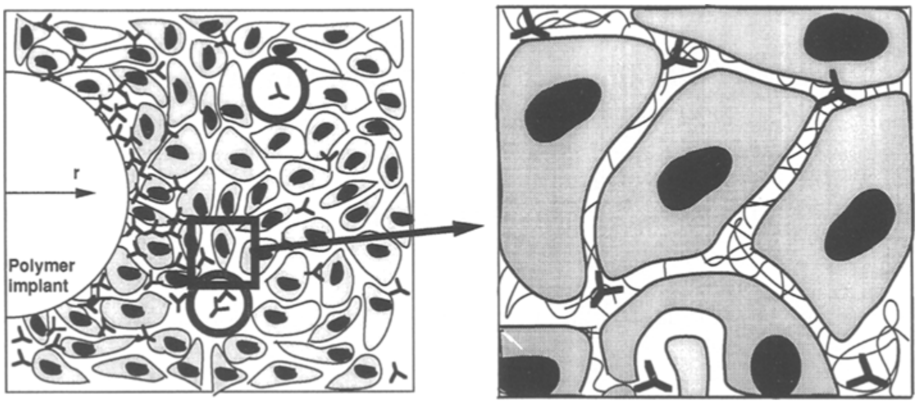

Fig. 1. The fate of the drug molecules in the brain interstitium upon release from a spherical polymeric implant is shown. Drug molecules that diffuse along the tortuous interstitial channels may be eliminated by a) non-specific binding to proteins, b) partitioning into the microcirculation, and c) metabolism before they reach the target site.

teristics for interstitially-delivered compounds. While our discussion focuses on drug transport in the context of polymeric controlled release, many of these issues apply to drug delivery to the brain by any of the approaches outlined in Table 1.

Controlled delivery systems for chemotherapy compounds

Polymer delivery systems for brain diseases

Recurrence of brain tumors following surgical resection is frequently local, suggesting that local therapy will be useful [6]. Controlled release polymeric implants are promising vehicles for interstitial chemotherapy because they provide a sustained and localized release of drug, while minimizing the systemic dose. A wide variety of polymer delivery systems have been developed; drugs for treating brain tumors and neurological disorders have been released from polymer matrices of different geometries, including microspheres, wafers, rods, capsules and pellets (see Table 2 for a partial list).

Kinetics of drug release from controlled release system

Polymer-based controlled delivery systems are drug reservoirs formed by enclosing, dispersing or dissolving the drug of interest within a solid polymer matrix. The kinetics of drug release from a typical controlled release system is frequently characterized by measuring the amount of drug released from the matrix into a well-stirred reservoir of phosphate buffered water or saline at 37° C. Controlled release profiles for three agents that may be useful for treating brain diseases are shown in Fig. 2; 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) is used clinically for chemotherapy of brain tumors, physostigmine is a cholinesterase inhibitor, and dexamethasone is used to treat peritumoral edema. The controlled release period can vary from several days to many months, depending on the drug and polymer chosen, and can be even longer (i.e. years) in many cases. A large number of studies have demonstrated that the delivery system can be tailored to the therapeutic situation by careful selection of implant properties as discussed below.

The release of drug molecules from polymer matrices is regulated by diffusion of drug through the polymer matrix or degradation of the polymer matrix. In many cases, including the release of BCNU from the degradable p(CPP-SA) matrix shown in Fig. 2, drug release from biodegradable polymers is diffusion-regulated, because the degradation time is much longer than the time required for drug molecules to diffuse through the polymer [7]. Only diffusion-regulated release is discussed here, since most degradable polymers provide release kinetics that are consistent with diffusion. In a few special cases linear release, which appears to correlate with the polymer degradation rate, can be achieved, however.

The amount of drug released from the polymer is proportional to the concentration gradient of the drug in the polymer. By performing a mass balance for drug within a differential volume element in the polymer, the concentration of drug within the polymer as a function of position and time can be described:

$$\frac{\partial C_p}{\partial t} = D_p \nabla^2 C_p \qquad (1)$$

where Cp is the local concentration of drug in the polymer, Dp is the diffusion coefficient of the drug in the polymer matrix, and t is the time following

Table 1. The advantages and disadvantages of several approaches to bypass the blood-brain barrier for drug delivery to the brain

Approaches to bypass BBB	Advantages	Disadvantages	Ref.
Controlled release from polymeric implants	• reduced systemic side effects • avoid peripheral drug inactivation and serum protein binding • no intervention required once the polymer is implanted	• dose adjustment difficult	7-11, 14-19
Transient osmotic disruption of BBB using hyperosmotic solution	• reversible • good for target tissues with a low blood flow in the infused artery or associated capillary bed • drugs with high plasma clearance biotransformation and excretion can be used	• exposing surrounding normal brain to high levels of drug • blood-tumor barrier permeability is highly dependent on the type of tumor • overdisruption result in malignant cerebral edema • a threshold event – require minimum osmolality and minimum duration of infusion	2,26
Infusion by pump delivery systems	• sustained delivery to the brain • no intervention required once pump has been implanted	• drugs must be stable and bioactive at 37° C when stored in saline or artificial cerebrospinal fluid • high rates of infection and malfunction of catheters • unpredictable release rates • intermittent infusion does not allow a sustained diffusion gradient • nonuniform drug distribution at slow infusion rates	2,27
High-flow microinfusion	• rapid and uniform tissue dosing • drug distribution is driven by bulk flow instead of diffusion, thus avoids high and even toxic drug concentration near the source • can dose larger volumes of brain tissue than low-flow delivery methods • stereotactic placement of the catheter causes minimal brain tissue damage	• infusate may leak back along the catheter shaft at large flow rates • possibility of inducing cerebral edema in the brain	5
Injection	• achieve regional specificity • minimal brain tissue damage • no complications due to peripheral actions of drugs which do not cross the BBB	• multiple injections required for drugs with short half-lives and chronic diseases	

immersion into the reservoir. This equation can be solved, with appropriate boundary and initial conditions, to obtain the cumulative mass of drug released as a function of time [8]:

$$M_t = 4M_o \sqrt{\frac{D_p t}{\pi L^2}} \qquad (2)$$

where Mo is the initial mass of drug in the polymer, and L is the thickness of the polymer. Figure 3 shows the cumulative mass of dexamethasone released (replotted from Fig. 2c), which increases linearly with the square root of time as predicted by Equation 2.

The macroscopic geometry, loading and formula-

Table 2. Examples of *in vivo* studies in which controlled delivery systems have been used to deliver drugs to the brain

Drug for brain disease	Disease treated	Delivery system	Ref.
Anticancer drug			
taxol	malignant glioma	p(CPP-SA)[a] 20:80 disc	28
methotrexate	malignant glioma	p(FAD-SA)[b] pellet	15
		pMMA[c] pellets	29
dexamethasone	peritumoral edema	pEVAc[d] pellet	8, 30, 31
5-fluorouracil	malignant glioma	pLGA[e] microspheres	32
		pMMA pellets	33
mitomycin	glioblastoma multiforme	pMMA needle-shaped	33
adriamycin	anaplastic astrocytoma	capsules	
ACNU[f] (minustine)			
bleomycin and lactose	craniopharyngioma	ethyl cellulose	34
4-hydroxyperoxy-cyclophosphamide	malignant glioma	p(FAD-SA) pellet	35
carboplatin	malignant glioma	p(FAD-SA) pellet	36
BCNU	malignant glioma	p(CPP-SA) pellet	21, 37
Angiogenesis inhibitor[g]			
heparin, cortisone	gliosarcoma	pEVAc	38
minocycline	tumor-induced	pEVAc	39
shark cartilage extracts	angiogenesis	pEVAc	40
Neuromodulator, Neurotransmitter			
dopamine	Parkinson's disease	pLGA microspheres	41
		silicone polymer pellet	42
		pEVAc pellet	43
		pEVAc rods	44
bethanecol	Alzheimer's disease	p(CPP-SA) microspheres	45
acetylcholine	Alzheimer's disease	polyanhydride microspheres	46
Peptides and proteins			
nerve growth factor	Alzheimer's disease	atelocollagen mini-pellet	47
		pLGA 70:30 microspheres	48
		pEVAc disc	16
Immuno-therapeutic agents			
IgG		pEVAc pellet	49
Others			
Monoganglioside GM1	brain lesion	human serum albumin microcapsules	50

[a] p(CPP-SA) = poly[bis(p-carboxyphenoxy)propane-sebacic acid].
[b] p(FAD-SA) = polyanhydride copolymer of fatty acid and sebacic acid.
[c] pMMA = poly(methyl methacrylate).
[d] pEVAc = poly(ethylene-co-vinyl acetate).
[e] pLGA = poly(DL-lactide-coglycolide).
[f] ACNU = 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride.
[g] Polymers incorporating the angiogenesis inhibitors were implanted in the rabbit cornea instead of the brain.

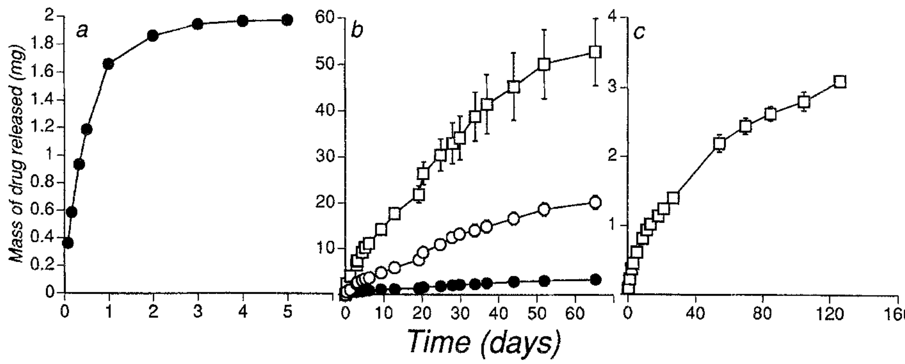

Fig. 2. The controlled release of a) BCNU (reproduced from 17), b) physostigmine at 50% (square), 40% (circle), and 30% (filled circle) loading (reproduced from 51), and c) dexamethasone (reproduced from 8) into well-stirred reservoirs of buffered saline is shown.

tion of the polymer matrices, as well as the physicochemical properties of the drug, affect the release kinetics. A uniform initial drug distribution in the polymer matrix produces release rates that decrease with time, because the drug diffusion distance from the matrix surface increases as drug molecules near the surface are released. High initial loading (i.e. mass fraction of drug particles within the matrix) usually results in faster release, due to the formation of larger channels or pores in the polymer matrix [9]. Loading can be increased by adding inert carriers (e.g. ficoll [10] and albumin) to produce diffusion channels when the drug is very potent. Properties of the polymer, like molecular weight [11] and composition [12], also influence the rate of release. Release rate usually increases with increasing particle size, presumably due to the formation of larger channels or pores in the polymer matrix [9]. The solubility of the drug in the release media affects the release rate as well [9].

Description of drug transport following release from a polymer

Once the polymer is implanted in the brain, drug molecules diffuse towards the polymer-tissue interface, either by migrating through the polymer or along channels created by dissolution of drug particles. Drug molecules are then released from the polymer, and diffuse through the brain tissue (Fig. 1). The relative resistance to diffusion in the polymer and migration in the tissue determines the rate of accumulation of drug molecules at the polymer-tissue interface and the rate of drug release from the polymer within the brain tissue. Within the tissue, the released drug molecules are transported by diffusion, which occurs at a rate proportional to the drug concentration gradient, and convection, which occurs at a rate proportional to the interstitial fluid velocity. Diffusion appears to be the dominant mode of drug transport in the extracellular space (ECS). The movement of the drug molecules through the network of interstitial channels in the brain is a complex process, which is similar to the hindered diffusion of a solute in liquid-filled, tortuous pores [13]. As the drug molecules penetrate the brain tissue and make their way to the target site, they may be eliminated by the action of enzymes, non-specific binding to proteins, or entry into the

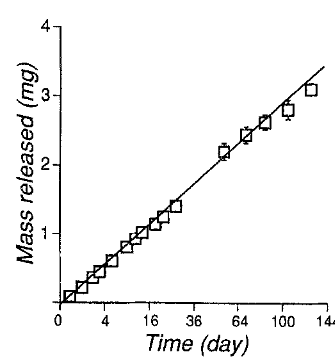

Fig. 3. The data from Fig. 2c are replotted versus the square root of time. The cumulative amount of dexamethasone released from p(EVAc) matrices increases linearly with the square root of time consistent with diffusion-controlled release.

systemic circulation by crossing the BBB. Drug molecules can also be internalized by brain cells before reaching the target site. Mathematical models describing the diffusion and elimination of drug upon release from the implant have been developed [7]. In this section, general equations for describing drug diffusion and elimination are developed, as well as simplifications of the general equations.

As in equation 1, a mass balance on a differential volume element in the tissue yields the general governing equation for drug transport in the region of the polymer:

$$\frac{\partial C}{\partial t} + \bar{v} \cdot \nabla C = D_b \nabla^2 C + R_e(C) - \frac{\partial B}{\partial t} \qquad (3)$$

where C is the concentration of the diffusible drug in the tissue surrounding the implant (g/cm^3 tissue), $\bar{v}$ is the velocity of extracellular fluid (ECF) (cm/s), D_b is the diffusion coefficient of the drug in the tissue (cm^2/s), $R_e(C)$ is the rate of drug elimination from the ECF, B is the concentration of drug bound or internalized in cells (g/cm^3 tissue), and t is the time following implantation. Equation 3 provides the local concentration of drug as a function of position and time, in the presence of a concentration gradient (diffusion) and the bulk flow of ECF (convection). D_b is an effective diffusion coefficient which accounts for the tortuosity (the 'windiness' of the path that a molecule must take to penetrate a given distance in the tissue), as well as any corrugations and constrictions in the pore volume. To simplify Equation 3, the following assumptions can be made:

1. ECF convection is negligible for most situations, where the interstitial fluid flow is small ($\bar{v} \approx 0$).
2. The concentration of intracellular or bound drug is directly proportional to the drug concentration in the tissue ($B = K_{bind} \cdot C$, where K_{bind} is the proportionality constant).
3. Drug is eliminated by a first order process with a lumped first order rate constant, k. Three types of elimination processes are modeled as first order: 1) partitioning into the microcirculation through the BBB, 2) enzymatic reactions which obey Michaelis-Menten kinetics at low substrate concentrations, and 3) nonenzymatic reactions.

With these simplifying assumptions, Equation 3 becomes:

$$\frac{\partial C}{\partial t} = D^* \nabla^2 C - k^* C \qquad (4)$$

where the apparent rate constant and diffusion coefficient are defined: $k^* = k/(1 + K_{bind})$ and $D^* = D_b/(1 + K_{bind})$. Equation 4 is the simplified governing equation of drug transport in brain interstitium; this equation applies equally well for both diffusion-regulated and degradation-regulated release from polymers.

The geometry of the polymer matrix determines the coordinate system used to solve Equation 4. Figure 1 shows the coordinate system for a spherical polymer implant in the brain. To solve for the concentration of drug as a function of position and time, two boundary conditions and one initial condition are required. In this case, we assume that the concentration of drug far from the polymer is negligibly small, and the initial concentration of the drug in the brain before implantation of the polymer equals zero. The second boundary condition depends on the mechanism of drug release from the polymer. Since the amount of the drug released from the polymer-tissue interface is equal to the amount of drug that reaches the polymer surface by diffusion, when the rate of diffusion of the drug in the tissue is much slower than the diffusion of drug within the polymer, the concentration of drug at the polymer/tissue interface is nearly constant [7].

Using these initial conditions and boundary conditions for a spherical polymer implant, the concentration profiles for transient diffusion and elimination are given by the following solution to Equation 4 [14]:

$$\frac{C}{C_o} = \frac{a}{2r} \left\{ \exp\left[-\left(r - a \sqrt{\frac{k^*}{D^*}} \right) \right] erfc \left[\frac{r-a}{2\sqrt{D^* t}} - \sqrt{k^* t} \right] + \exp\left[(r-a) \sqrt{\frac{k^*}{D^*}} \right] erfc \left[\frac{r-a}{2\sqrt{D^* t}} + \sqrt{k^* t} \right] \right\} \qquad (5)$$

where a is the radius of the spherical implant and C_o is the concentration of drug at the polymer-tissue interface. After sufficient time has passed, the con-

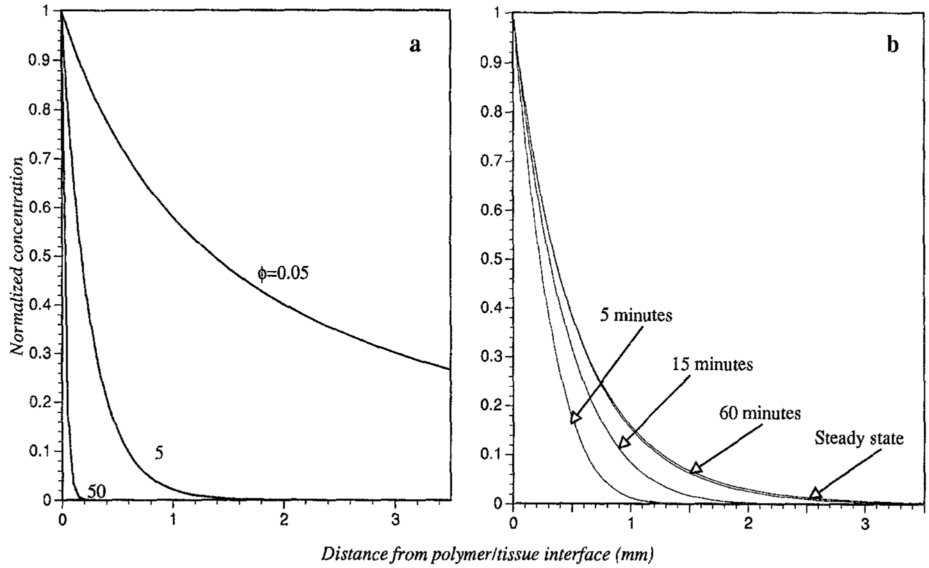

Fig. 4. a) The effect of the modulus, ϕ, on the normalized concentration profiles obtained by solving Equation 6 for the steady-state diffusion and elimination. Smaller values of ϕ indicate slower drug elimination, and therefore larger penetration distances in the brain tissue. b) The approach to steady-state is indicated for a modulus value $\phi = 2$.

centration profile reaches the following steady-state:

$$C = \frac{C_0 a}{r} \exp\left(-\phi\left(\frac{r}{a} - 1\right)\right) \qquad (6)$$

where ϕ is a dimensionless parameter, $a\sqrt{k^*/D^*}$, which is equal to the ratio of the rate of elimination to the rate of diffusion of the drug in the brain. This modulus, ϕ, which depends on the physical, chemical, and biological characteristics of the drug, determines the extent of penetration of drug from the polymer interface and the time to reach steady-state [7]. For larger values of ϕ, the distance for drug penetration is shorter. Typical concentration profiles obtained from Equations 5 and 6 for different values of ϕ are shown in Fig. 4. Profiles predicted by this equation have been compared to concentration profiles measured for a variety of molecules delivered by polymers to the brain – dexamethasone [7, 8], molecular weight fractions of dextran [15], nerve growth factor in rats [16], BCNU in rats [17], rabbits [14] and monkeys [18] – and appears to capture most of the important features of drug transport. Some typical values of ϕ, consistent with these experimental measurements, are shown in Table 3 [14, 19].

Table 3. ϕ^2_{SS} is the square of the modulus, a^2k^*/D^*, obtained from the steady state solution to the diffusion/elimination model, as shown in Equation 6. ϕ^2_{SS} of BCNU, IAP and dextran were determined 24 hours after the polymer was implanted. ϕ^2_{SS} of nerve growth factor was determined 48 hours after the polymer was implanted

Agent	ϕ^2_{SS}	Ref.
IAP[a]	13	14
BCNU	5.4	14
Nerve Growth Factor	1.6	14
Dextran	0.81	19

[a] IAP = iodoantipyrine.

For a drug to be effective, it must penetrate through the tissue and move away from the polymer to reach a site of action. For reasonable values of the modulus ϕ, our model predicts that drug penetration will be limited to a 1–3 mm region near the polymer implant. The penetration distances of several agents delivered to the brain by controlled release systems and other methods are shown in Fig. 5. Regardless of the delivery system, the distances that these agents penetrate are very small compared to the size of human brain. A notable exception is dextran, which appears to migrate much farther than any of the other compounds.

While this diffusion/elimination model compares

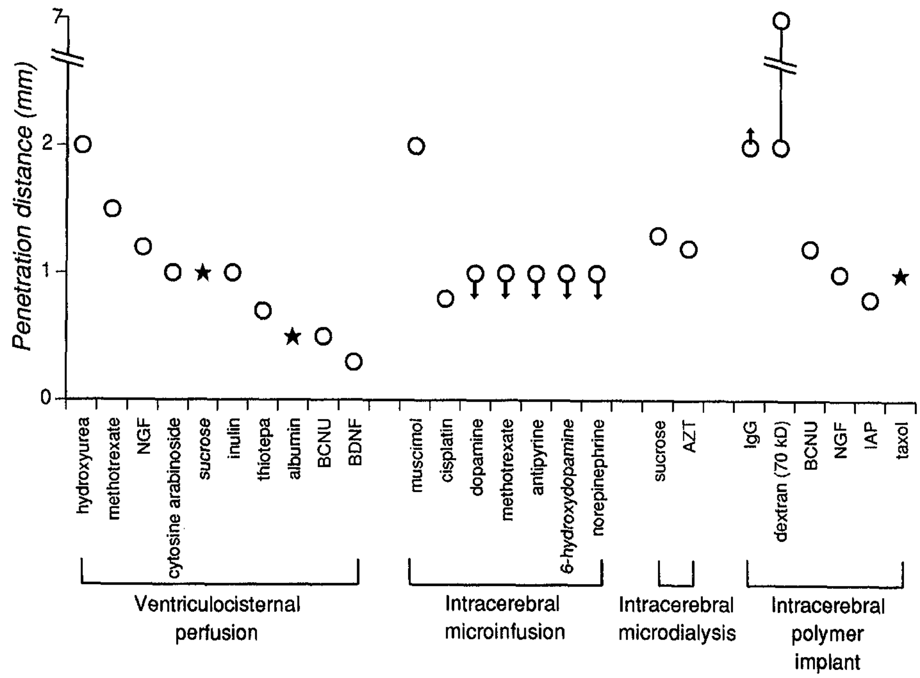

Fig. 5. Penetration distances for agents administered to the brain by ventricular cisternal perfusion, microinfusion, microdialysis, or polymer implantation. In this report, penetration distance was assumed to equal the distance measured from site of administration to the point where drug concentration in the brain tissue dropped to 10% of the maximum value. Penetration distances were determined from literature reports, or described in another report [14]. In many cases, only approximate penetration distances could be determined (star). In other cases a lower bound (circle with arrow pointing upward) or upper bound (circle with arrow pointing downward) on the penetration distance was obtained. Data are compiled from Ref. 14, 19, 28, 49, 52–61). BDNF = brain derived neurotrophic factor, AZT = azidovudine, NGF = nerve growth factor.

very well with available experimental data, the assumptions used in predicting the concentration profiles in the brain may not be appropriate in all cases. Deviations from the predicted concentration profiles may occur due to extracellular fluid flows in brain, complicated patterns of drug binding to extracellular proteins or other tissue components, or complicated multistep elimination pathways. The motion of interstitial fluid in the vicinity of the polymer and the tumor periphery may not always be negligible, particularly in the region of a tumor. The interstitial fluid velocity is proportional to the pressure gradient in the interstitium [20]; higher interstitial pressure in tumors – due to tumor cell proliferation, high vascular permeability, and the absence of functioning lymphatic vessels – may lead to steep interstitial pressure gradients at the periphery of the tumor [20]. As a result, interstitial fluid flows within the tumor may influence drug transport. A drug at the periphery of the tumor must overcome outward convection to diffuse into the tumor [20]. Furthermore, local edema after surgical implantation of the polymer may cause significant fluid movement in the vicinity of the polymer. Local edema appears to occur from surgical trauma alone; for example, edema persisted for 14 days after surgery in the monkey brain, and did not appear to increase in the presence of an empty or a BCNU-loaded p(CPP-SA) pellet [21]. Improved mathematical models that include the convective contribution to drug transport are required and are being developed [17, 18, 22]. While the convective flow contribution to drug transport may not be negligible, especially for macromolecules, measurement of fluid velocity *in vivo* is difficult. Improved, noninvasive methods for quantifying fluid movement are needed to evaluate this matter completely.

The metabolism, elimination and binding of drug are assumed to be first order processes in our simple analysis. This assumption may not be realistic in all cases, especially for complex agents, such as antibodies that target tumor-associated antigens. The metabolism of antibodies in normal and tumor tissues is still poorly understood. In addition, antibody concentration profiles are affected by a number of factors including molecular weight, binding affinity, antigen density, vascular permeability, metabolism, and heterogeneity within the tumor [23]. Other cellular factors (e.g. the heterogeneity of tumor-associated antigen expression and multidrug resistance) that influence the uptake of therapeutic agents may not be accounted for by our simple first order elimination.

Finally, changes in the brain that occur during the course of therapy are not properly considered in this model. Irradiation can be safely administered when a BCNU-loaded polymer has been implanted in monkey brains [21], suggesting the feasibility of adjuvant radiotherapy. However, irradiation also causes necrosis in the brain. The necrotic region has a lower perfusion rate and interstitial pressure than tumor tissue [20], thus the convective interstitial flow due to fluid leakage is expected to be smaller. Interstitial diffusion of macromolecules is lower in normal tissue and higher in tumor tissue as the latter has larger interstitial space [20]. The progressive changes in tissue properties – due to changes in tumor size, irradiation, and activity of chemotherapy agent – may be an important determinant of drug transport and effectiveness of therapy in the clinical situation.

New approaches to drug delivery suggested by the model

Our simple mathematical model, which describes the diffusion and elimination of drug following controlled delivery in the brain, allows us to predict the penetration distance of the drug, the length of the controlled release period, and the amount of drug released at a particular time. As mentioned previously, a small value of the modulus ϕ indicates that the rate of drug elimination is small relative to the rate of drug diffusion; small ϕ is characteristic of a drug that can penetrate further into the brain tissue. In light of this, when one selects drugs for controlled delivery in the brain, drugs that are slowly eliminated are preferred. The modulus ϕ provides a quantitative criterion for selecting agents that are best suited for interstitial delivery.

As an example of this concept, high molecular weight, water-soluble molecules (e.g. dextran) were retained longer in the brain space, and distributed to a larger region of the brain, than low molecular weight molecules following release from an intracranial implant. This suggests a strategy for modifying molecules to improve their penetration in the brain [24]. By conjugating an active drug to polymers which serve as inert carriers, the rate of drug elimination should be reduced. For instance, anticancer drugs and neuropeptides can be conjugated to proteins, antibodies or other inert carriers for targeting radioisotopes or drugs to cells, specialized endothelia, and normal and neoplastic tissues expressing the corresponding binding sites [25]. For conjugated drugs, the extent of penetration should depend on the modulus ϕ for the conjugated compound and the stability of the linkage. Several factors influence the stability of the linkage between the drug and the polymer carrier: the type of spacer, the sensitivity of the linkage to hydrolysis, the pH of the solution, the route of conjugate delivery, and the amount or dose of agent attached to the polymer [15].

The effects of conjugation and stability of the linkage between drug and carrier on enhancing tissue penetration in the brain have been studied in a model system [15]. Methotrexate (MTX)-dextran conjugates with different dissociation rates were produced by linking MTX to dextran (molecular weight 70,000) through a short-lived ester bond (half-life $\approx$ 3 days) and a longer-lived amide bond (half-life > 20 days). The extent of penetration for MTX-dextran conjugates was studied in three-dimensional human brain tumor cell cultures; penetration was significantly enhanced for MTX-dextran conjugates and the increased penetration was correlated with the stability of the linkage. These results suggest that modification of existing drugs may increase their efficacy against brain tumors when delivered directly to the brain interstitium.

Conclusion

From the studies performed to date, it is clear that controlled release polymers provide a useful method for delivering drugs directly to the brain interstitium. This approach may improve the therapy of brain tumors or other neurological disorders. Still, many important questions relevant to the design of optimal delivery systems for humans remain unanswered. What is the relationship between release from the polymer and dose delivered to the brain? How far must the drug penetrate the brain tissue to be effective? How will fluid motion in the brain interstitium influence drug transport and distribution? The mathematical model described in this paper provides a useful framework for evaluating these issues and should, ultimately, allow us to predict the spatial and temporal distribution of drug in brain interstitium.

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