Extended Levodopa Release from a Subcutaneously Implanted Polymer Matrix in Rats

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It is well recognized that plasma fluctuations resulting from oral levodopa therapy may cause an unstable clinical response in parkinsonian patients. We have therefore developed a slow-release polymer matrix system that can deliver levodopa continuously for extended periods of time (at least 225 days) after subcutaneous implantation in rats. Advantages of this approach include (1) the elimination of levodopa plasma fluctuations and (2) the possibility of reducing the required dose due to constant plasma levels and because the gastrointestinal tract is circumvented. The peripheral implantation of polymer systems containing levodopa, dopamine receptor agonists, or other anti-Parkinson agents may constitute a novel technology of drug delivery to improve the care of patients with Parkinson's disease.


The majority of parkinsonian patients show a reasonably stable clinical response to oral levodopa (L-Dopa)

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therapy, despite plasma L-Dopa fluctuations [1, 2]. After several years of therapy, the patient responses begin to fluctuate, and L-Dopa treatment is less effective [3]. In many patients, these clinical fluctuations are parallel to fluctuations in plasma L-Dopa levels [3, 4], and it is therefore desirable to obtain constant plasma levels of L-Dopa through improved modes of drug delivery. A variety of methods have been developed to date for the improved delivery of L-Dopa or dopamine receptor agonists. They include intraventricular infusion [4, 5], implantable or external reservoir pump systems [6], and oral slow release preparations such as Sinemet CR3 - CR5 [7, 8] and Madopar HBS [9] as well as others [10-13]. Although each approach appears to provide some benefits, none of them combines convincing features of practicability with unequivocal efficacy. We have therefore developed a peripherally implantable controlled-release polymer system, and we now document continuous L-Dopa delivery in rats for more than 200 days after subcutaneous implantation.

Methods
Ethylene vinyl acetate copolymer (EVA) containing 70% (w/w) L-Dopa (Sigma Chemical, St. Louis, MO) was prepared by using a method similar to one described previously [14], resulting in rectangular samples (15 × 30 × 2 mm, total weight 1.3 g). Figure 1A displays a schematic to illustrate the polymer composition and mechanism of drug release. Figure 1B shows a cross-section through one such polymer matrix containing L-Dopa crystals by using scanning electronmicroscopy (SEM, magnification × 300). Based on in vitro observations (see also [14]), we expected a non-coated polymer matrix with 70% loading to provide a maximal release rate. Therefore, in vitro release of L-Dopa from such samples was monitored by using spectrophotometric analysis in conjunction with high performance liquid chromatography (HPLC) (see legend of Fig 2A).

For the in vivo experiment, three Male Sprague-Dawley rats (250-360 gm) were anesthetized with ether, and an L-Dopa-containing implant (70% loading) was inserted subcutaneously through a small incision into each rat. A control rat received an unloaded implant (without L-Dopa). On the day after implantation and at various times thereafter, 700 to 800-μl blood samples were drawn from the tail vein (ether anesthesia), collected in vials containing 20 μl glutathione-ethylenediaminetetraacetic acid solution (pH 6-7), vortexed, and centrifuged at 4°C for 10 minutes at 4,000 rpm. Plasma was then stored at -70°C until samples were assayed for catecholamines by using HPLC according to a previously published method [15] (see also legend of Fig 2).

Results
SEM analysis at × 300 (see Fig 1B) shows L-Dopa crystals embedded in the polymer matrix. The matrix contains small channels and pores through which L-Dopa dissolves into the aqueous environment. Spectrophotometric evaluation of in vitro release revealed continuous L-Dopa release for at least 225 days. After subcutaneous implantation, the mean plasma L-Dopa level was relatively high in the initial period of release, ranging from 220 to 700 ng/ml (mean of 480 ng/ml, see Fig 2B). After about 50 days, this level decreased by approximately 90%, and release approached linearity thereafter. In 1 rat, zero-order kinetics were
achieved, with a release of at least 8 ng L-Dopa/ml from Day 84 through at least Day 225, at which time the experiment was terminated. The control rat had a mean plasma L-Dopa level of 1.66 ± 0.16 ng/ml. Thus, the polymer implants resulted in continuous L-Dopa release to obtain stably elevated plasma L-Dopa levels in vivo for more than one-half year, which were fourfold to eightfold higher than control levels. The release kinetics in vivo (see Fig 2B) are very similar to those observed in vitro (see Fig 2A).

Discussion
Numerous investigators have now shown that continuous delivery of L-Dopa constitutes the best mode of treatment for parkinsonian patients, and a number of methods have been developed to obtain improved drug delivery. Using a controlled release polymer matrix system, we have now obtained L-Dopa release for an extended period of time (more than 225 days). After subcutaneous implantation in rats, this approach results in stable L-Dopa levels of at least fourfold to eightfold above normal. Using the same polymer matrix system, we have also previously reported that extended delivery of dopamine can be obtained both in vitro and in the brain [14, 16].

The following are several reasons suggesting that our polymer system is potentially valuable for the controlled delivery of anti-Parkinson agents: (1) it appears that both the rate of release and the service lifetime of the peripheral implants are adequate, (2) the polymer matrices are biocompatible, (3) sustained release eliminates the drug plasma fluctuations, and (4) circumvention of the gastrointestinal tract may permit a significant reduction in dose. This is supported by the observation that when infused through duodenal tubes in human parkinsonian patients, the 24-hour dose requirement for L-Dopa is decreased significantly [13].

Yet, other advantages of our approach are that (5) drugs (such as L-Dopa) embedded in polymer matrices have long-term biological activity exceeding that of drugs that are suspended in solution as, for example, with reservoir pumps, (6) the polymer can easily be replaced or removed if medical or psychiatric problems arise, and (7) the polymer implants can eliminate the compliance problems seen in some patients.

It can be argued that polymer implants do not provide sufficient flexibility to adjust the dose for an individual patient. An appropriate daily dose of L-Dopa for a particular patient could first be determined, however, by using intravenous duodenal infusion, followed by selection of an appropriate polymer sample and subsequent implantation into patients in an ambulatory setting.

Implants are expected to benefit primarily patients with response fluctuations, that is, patients in the later
stages of the disease, but polymer implants, due to their virtue of keeping the dose constant and relatively low, may also be able to retard or preclude the appearance of the "on-off" and "end-of-dose" responses when implanted early in the disease. Thus, peripheral implantation of polymer matrices containing L-Dopa or dopamine receptor agonists might comprise a useful method of drug delivery to improve the treatment of Parkinson's disease.

References

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