

Adenosine-releasing silk-based brain implants for epilepsy therapy

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Silk-based brain implants engineered to release the brain's own anticonvulsant adenosine prevent the development of epileptic seizures in rats. The combination of two naturally occurring compounds (silk and adenosine) into one therapeutic implant holds promise for future applications in epilepsy therapy. About 3 million Americans are affected by epilepsy, one of the most frequent neurological disorders. Roughly one third of those patients cannot be treated with conventional drugs or surgery due to ineffectiveness or intolerable side effects. Therefore, new therapeutic strategies are urgently needed. Seizure activity is regulated by adenosine, an endogenous "protector" of the brain. During the process that leads to epilepsy the adenosine system gets out of order and reduced levels of adenosine contribute to seizure development. As a rational therapeutic approach, we propose to reconstitute the adenosine system in epilepsy with adenosine releasing polymer-based brain implants. Our results suggest that a local brain implant of adenosine-releasing silk-based polymers is effective in preventing seizures and possibly the development of epilepsy. This is the first demonstration that a combination of the two FDA approved compounds – silk and adenosine – is effective therapeutically.

To develop brain implants for the local release of a defined dose of adenosine, we embedded adenosine containing microspheres into nanofilm coated silk fibroin scaffolds. Our devices were designed to release target doses of 40, 200, and 1000 ng adenosine per day over a time span of 2 weeks. These polymers were implanted into the brains of rats into close proximity to an epilepsy sensitive brain area. During a time span ranging from 4 to 20 days after polymer implantation this epilepsy-sensitive brain area was repeatedly stimulated electrically to artificially induce epilepsy-like seizures. In control rats, which received a silk polymer that did not release adenosine, this procedure resulted in robust seizure development within 10 days. During these repeated stimulations epilepsy develops gradually; thus, the development of epilepsy can be closely monitored in this animal model.

Our results show that adenosine releasing brain implants prevented the development of epilepsy in a dose-dependent way. Animals receiving the implant that was designed to release 1000 ng per day were completely protected from convulsive seizures during the life-span (14 days) of the polymers; after expiration of the polymers (from day 14 to day 20), epilepsy development resumed at a normal pace suggesting that suppression of epilepsy development was due to adenosine released from the polymers.

Our data describe a novel silk-based delivery system for adenosine that fulfills crucial requirements for future clinical application, such as: (i) biocompatibility, (ii) delivery of predetermined doses of adenosine, (iii) safety as opposed to transplantation using animal cells, (iv) sustained function via slow degradation of the polymer, and (v) therapeutic efficacy in a widely used preclinical model for the development of epilepsy that has a high predictive value in drug

development. Most importantly, our study for the first time defines minimally effective doses in the range of 50 to 200 ng adenosine per day, and suggests that focal delivery of adenosine might not only have therapeutic value for the suppression of established seizures, but also for the prevention of epileptogenesis.

Adenosine augmentation therapies (AATs) constitute a novel approach to suppress seizures in epilepsy and possibly to prevent the development of epilepsy. Unfortunately, AATs cannot be given as a “pill”, which would lead to adenosine-related side-effects throughout the body. However, when delivered to a specific site within the brain, adenosine – as an endogenous seizure protector of the brain, with efficacy in drug-resistant epilepsy – will augment the brain’s own seizure control mechanisms with the promise to be devoid of major side effects. Our study, using a combination of the two FDA approved compounds adenosine and silk, is expected to move the field forward towards the design of first clinical trials. Intellectual property:

- United States Patent 6110902: “Method for the inhibition of neuronal activity leading to a focal epileptic seizure by local delivery of adenosine”; Inventors: Mohler, Hanns; Boison, Detlev; Application Number: 08/881038; Publication Date: 08/29/2000; Filing Date: 06/23/1997;
- WIPO Patent Application WO/2009/140588: “Silk polymer-based adenosine release: therapeutic potential for epilepsy”; Inventors: Boison, Detlev; Kaplan, David L.; Application Number: PCT/US2009/044117; Publication Date: 11/19/2009; Filing Date: 05/15/2009

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