Evaluation of the antifibrotic effect of paclitaxel (PTX) and caffeic acid phenethyl ester (CAPE) in a rat model

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Purpose

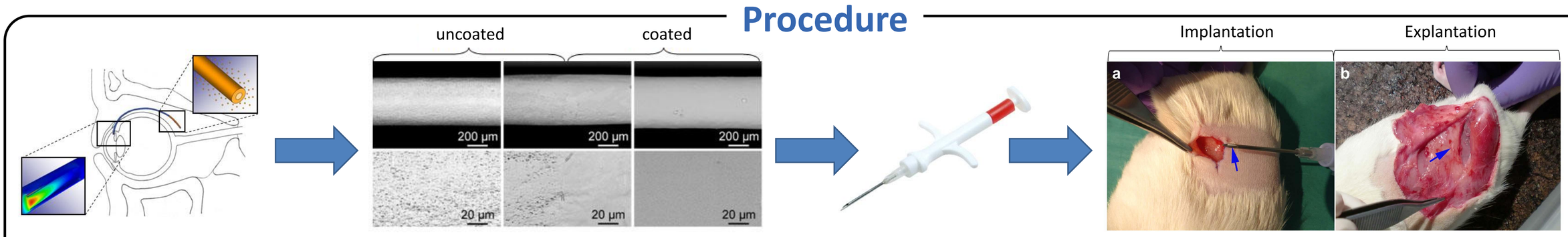
Fibrotic processes following glaucoma microstent implantation are the major factor for a postoperative decrease in liquid drain. Thus, development of an antifibrotic drug eluting microstent to lower IOP is one of the most important clinical goals. This study aimed at the antifibrotic effects of paclitaxel (PTX) and caffeic acid phenethyl ester (CAPE) in a rat model. Here, we investigated the postoperative influence of drug coated test specimen on the fibrotic response in subcutaneous white fat depots in rats.

Methods

Drug coated or uncoated test specimens were implanted by a minimal invasive surgery in the subcutaneous white fat depot in front of the right hind leg. At defined postoperative time points (1-36 weeks) fat depots were explanted, fixed and prepared for histological investigation.

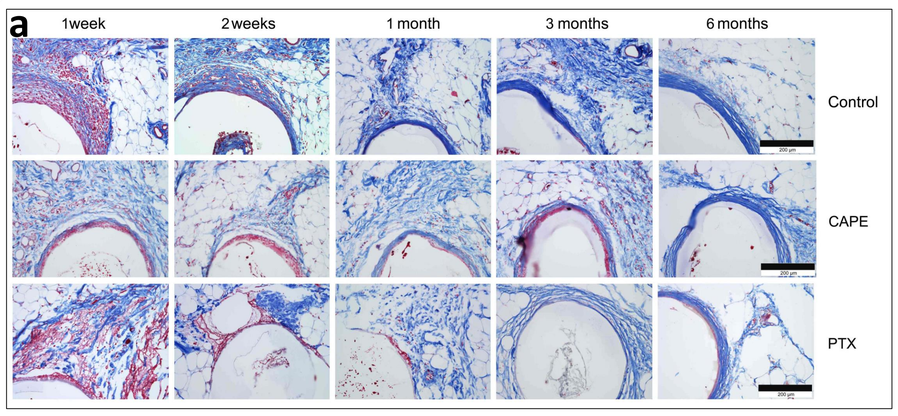
Histological sections of 5 µm thickness were AZAN and HE stained, or detailed investigation of immunohistochemistry was carried out using the standard protocols to analyze the fibrotic response.

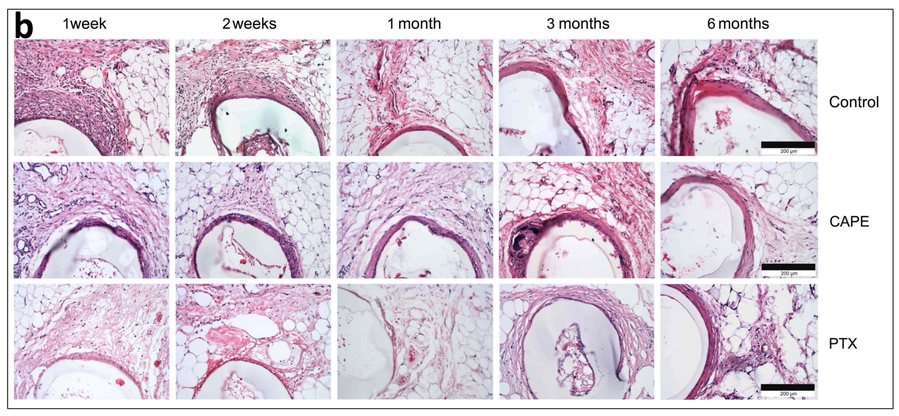
Procedure



Stent concept — Specimen: P(4HB)/at.P(3HB), Ø=450µm, l=10mm — Injector — Surgery

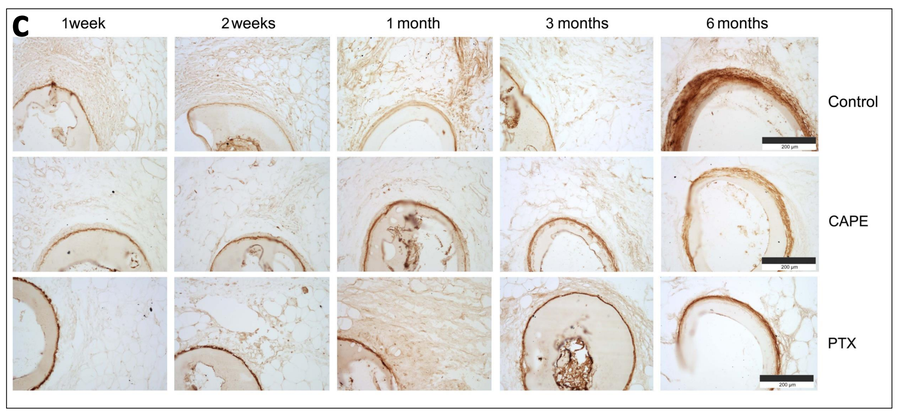
Results

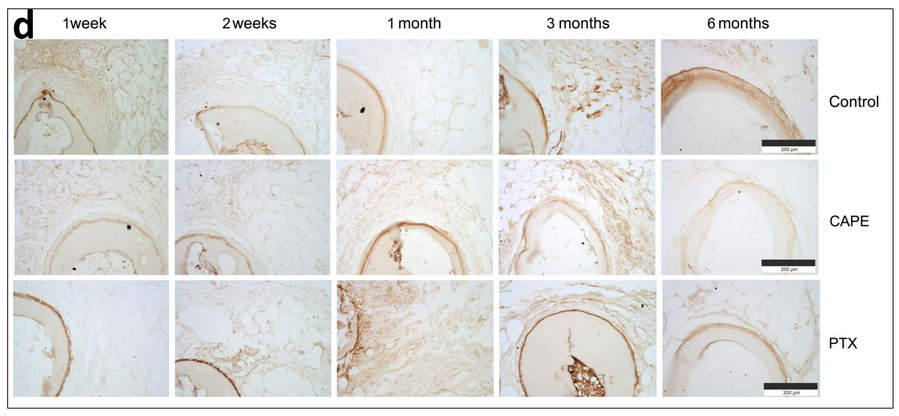




Histology of the white fat depots including the test-specimen-implants: The Cross sections of the rat fat depots were stained for connective tissue using AZAN **(a)** and hematoxylin/eosin (HE) staining **(b)**.

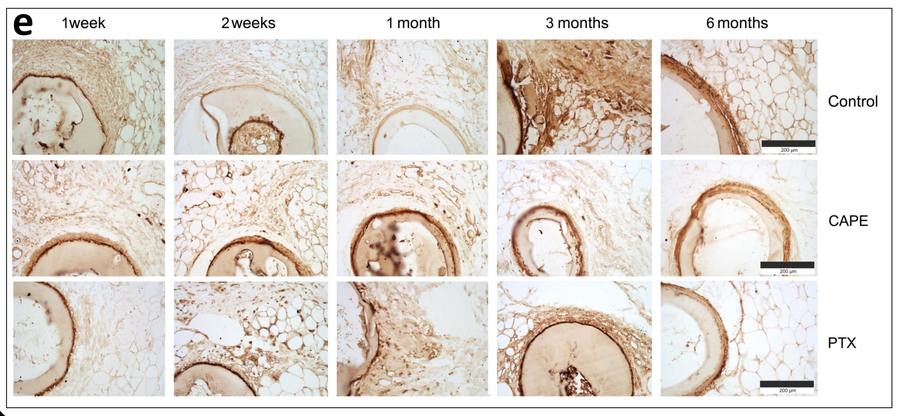
A connective tissue-rich fibrotic capsule is obvious after 6 months in the periphery of uncoated control implants, as well as in the CAPE and PTX coated specimens.

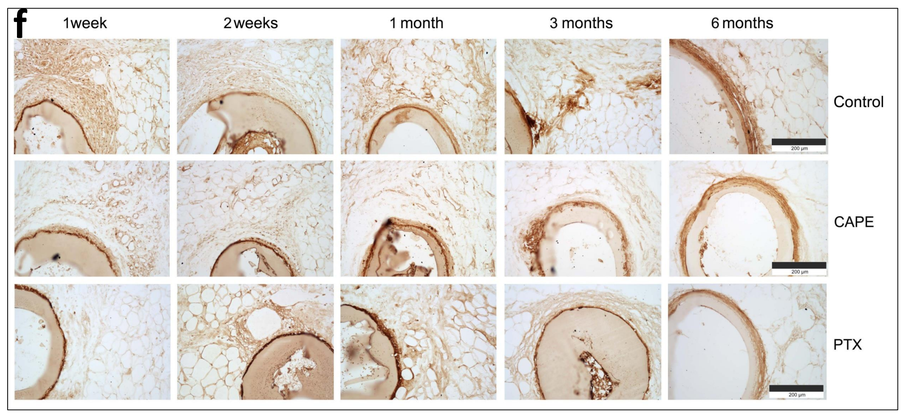




Immunohistochemistry of the white fat depots including the test-specimen-implants: The Cross sections of the rat fat depots were stained for collagen I **(c)** and collagen III, respectively **(d)**.

The connective tissue-rich fibrotic capsule is positive stained for collagen I. Only a faint expression of collagen III could be detected after 6 months around the uncoated control and the drug-coated implants.





Immunohistochemistry of the white fat depots including the test-specimen-implants: The Cross sections of the rat fat depots were stained for collagen VI **(e)** and fibronectin, respectively **(f)**.

The connective tissue-rich fibrotic capsule is positive stained for collagen VI. Also a strong expression of fibronectin could be detected after 6 months around the uncoated control and the drug-coated implants.

Conclusions

Histological analyses of subcutaneously implanted drug coated test specimens opens up new possibilities to investigate the release kinetics of novel antifibrotic agents *in vivo*. Additionally, the antifibrotic potential as well as their side effects could be analyzed by immunohistochemistry. We could show that CAPE could not prevent the formation of a fibrotic capsule. Also the PTX coated test-specimen failed after six month but an antifibrotic effect was obvious at earlier time points, unfortunately accompanied with side effects. In conclusion, these investigations will pave the way to detect effective but harmless antifibrotic agents with reduced side effects to optimize IOP reducing drug eluting microstents.

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Potentielle Interessenkonflikte: 1. nein, 2. nein, 3. nein, 4. nein, 5. nein