Blocking Substance P Signaling Inhibits the IL-6 Transcription Induced by a Single Dwell in a Rat Model of PD

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Conclusions

The model discriminated between the effects of catheter implantation (IL-1 induction) and PD fluid exposure (IL-6 induction). In clinical materials, IL-6 levels correlate with peritoneal transport and high levels of IL-6 are associated with adverse changes of the peritoneal membrane. In the present model IL-6 transcription was counteracted by SP receptor blocking, suggesting that SP may be involved in mechanisms that are closely connected to the development of membrane transformation in PD.

Introduction and Objectives

The development of modern biocompatible peritoneal dialysis (PD) fluids has not eliminated adverse tissue reactions of the peritoneal membrane. Neurogenic inflammation, where osmotic stimulation of mechano-sensing nerves leads to the liberation of substance P, is a possible triggering mechanism with a potential to drive cytokine release that maintains a state of peritoneal inflammation, leading to fibrosis and angiogenesis.

The present study evaluated the transcription of specific cytokines during a single PD dwell and the effects of substance P receptor (NK1) blockade.

Methods

Single 4-hour 20 ml PD dwells of filter-sterilized, lactate-buffered, 2.5% glucose PD fluid were performed in rats with previously implanted PD catheters. Dialysate samples were collected for measurements of cytokine concentrations. Transcription of cytokines IL-1 beta, IL-6, TNF-alpha in relation to housekeeping gene beta-actin was quantified by qPCR on RNA extracts from abdominal muscle biopsies. PD with and without pre-treatment with the substance P receptor (NK1) blocker Spantide II was compared with untreated animals and animals with implanted PD catheter but no PD treatment.

Results

The transcription of IL-1 beta increased significantly after implantation of the PD catheter but not further after a subsequent PD dwell. IL-6 transcription, on the contrary, was not significantly affected by catheter implantation but increased significantly (4-fold induction) after a PD dwell (Fig. 1). Transcription of TNF-alpha did not differ signi-ficantly between the groups. The mRNA levels for IL-6 were restored by treatment with the Substance P receptor (NK1) blocker Spantide II (Fig. 1).

Dialysate concentration changes of IL-6 over PD dwell time showed a non-significant trend ($p<0.1$) towards lower levels in animals pretreated with substance P receptor blockade (Fig. 2).

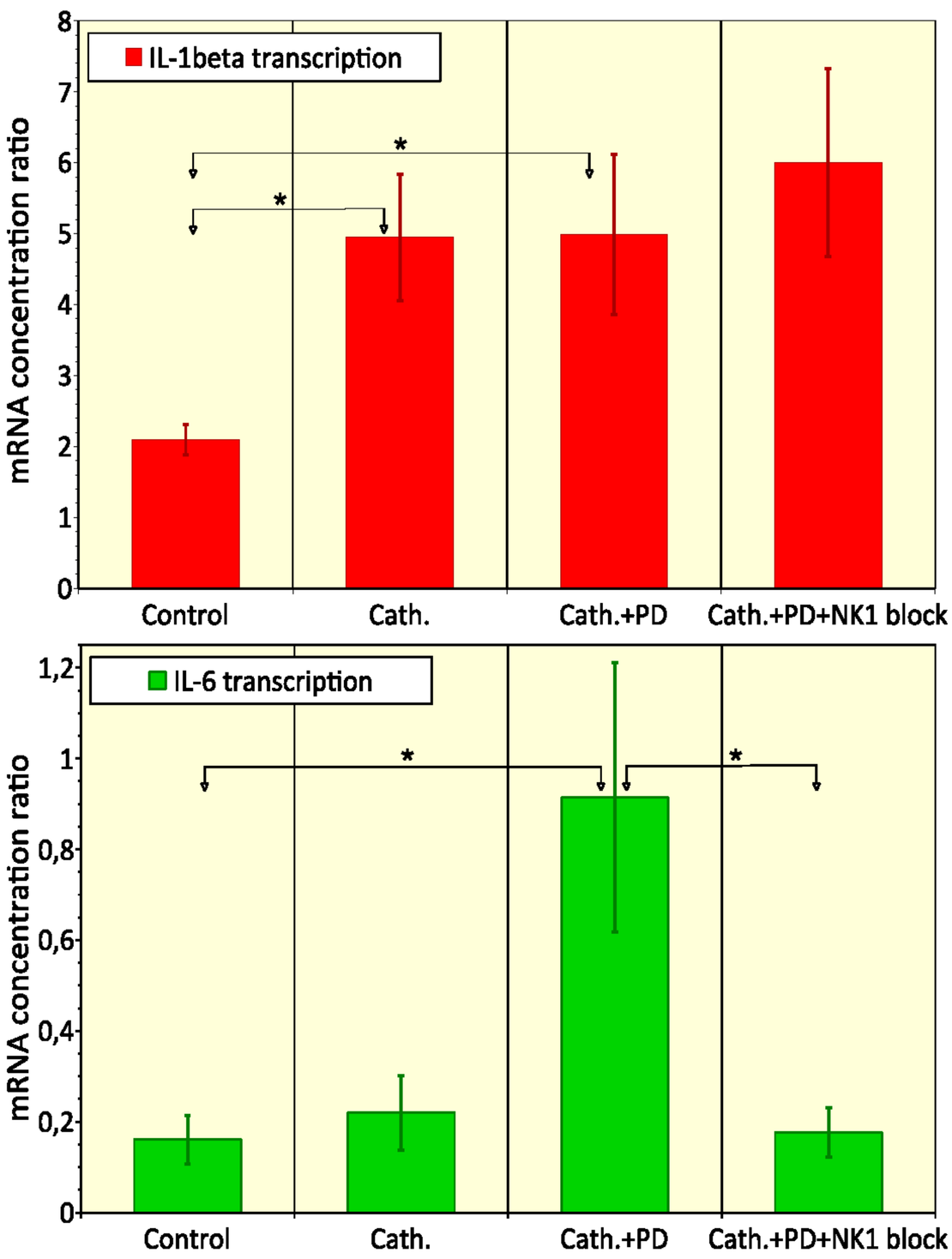

Figure 1: Transcription (mean±SEM) of IL-1 (upper panel) and IL-6 (lower panel) in peritoneal biopsies from untreated animals (Control), animals with implanted PD catheters, either exposed to a 4-hour PD dwell (Cath.+PD) or not (Cath.). In a separate group, animals with PD catheter were pretreated with the NK1 blocker Spantide II immediately before the PD dwell (Cath.+PD+NK1 block). * Significant differences ($p<0.05$).

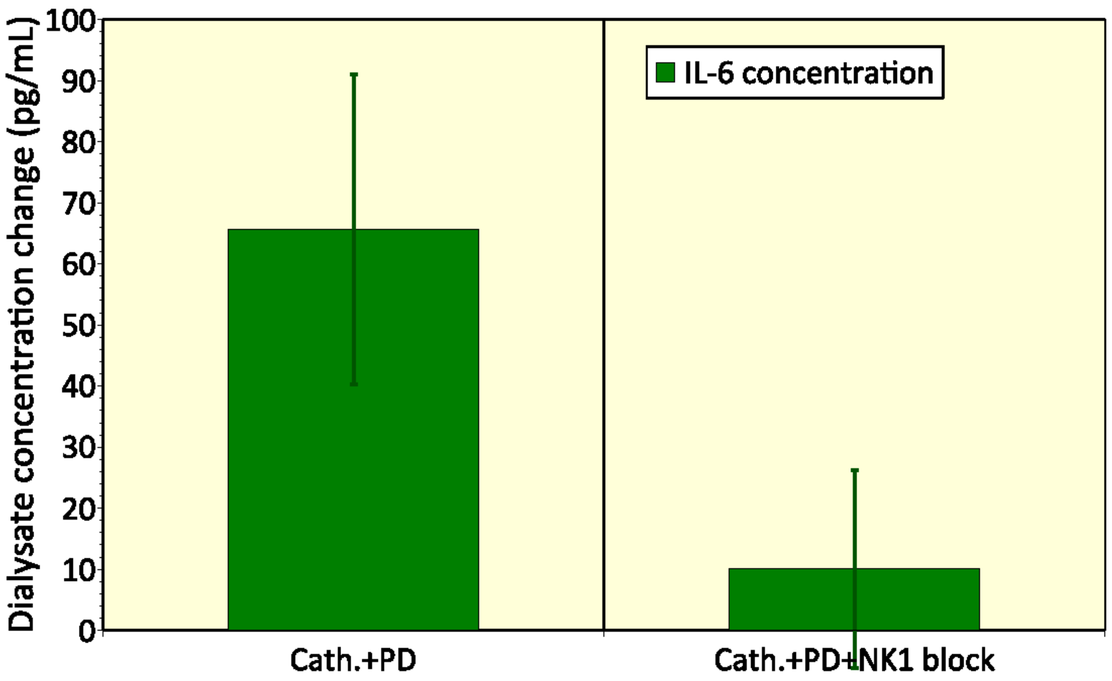

Figure 2: Concentration change (mean±SEM) of IL-6 over a 4-hour PD dwell without pharmacological pretreatment (Cath.+PD) and with pretreatment with the NK1 blocker Spantide II immediately before the PD dwell (Cath.+PD+NK1 block). No significant difference was found.

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