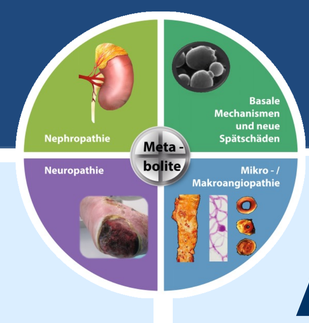
SFB 1118 Reaktive Metabolite als Ursache diabetischer Folgeschäden



Methylglyoxal (MG)-derived carbonyl stress in sepsis

(DFG Reference-No.: BR 4154/2-1)

AP

Schmoch/ Brenner

Metabolite:
Methylglyoxal (MG) (+Glyoxal (G))

Posttranslational Modification:
MG- & (G)-induced AGEs

Metabolic Pathway:
MG-formation ↑ (Regulation of glycolytic key-enzymes) vs. MG-detoxification ↓ (GLO-dependent detoxification)

Complication:
Sepsis, Septic shock, Predispositions for sepsis

Interactions

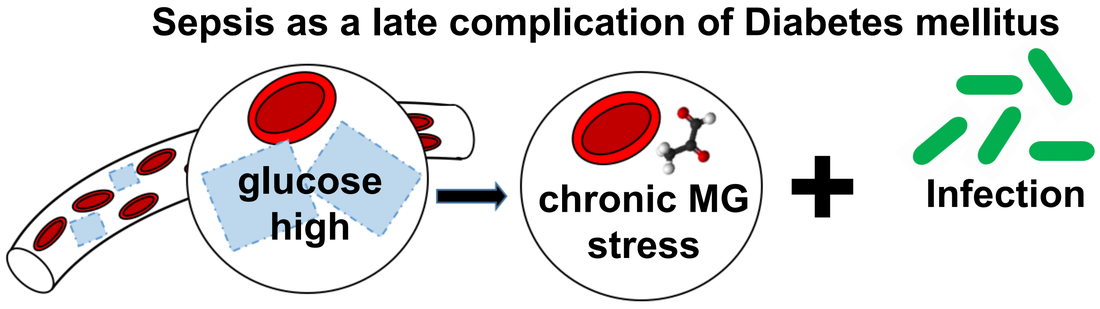
A02 – Liver as a novel complication
A04 – Diabetes mouse models
B01 – Akt signaling
B06 – ROS-dependent PTM
C06 – DNA damage and repair
C07N – Resistance pathways
S01 – TSC22D4 metabolome
S02 – TSC22D4 in humans
KS01 – Liver markers

Questions

1. **Which organs and which cell entities are the main sources of MG-derived carbonyl stress in sepsis?**
   - Endogenic vs. exogenic (e.g. bacterial synthesis of MG) sources?
   - Which mechanisms are responsible for the fast increase of MG plasma levels in sepsis?
2. **Does MG-derived carbonyl stress influence the course of the disease in sepsis?**
   - Which mechanisms are responsible for MG-caused damages?
   - Is it possible to modify MG-derived carbonyl stress therapeutically?

Outlook

Sepsis as a late complication of Diabetes mellitus



➔ **increased likelihood of sepsis and septic shock**

Hypothesis: Sepsis ➔ endogenic MG-formation ⇧ + MG-detoxification ⇩ ➔ mortality ⇧(causal)

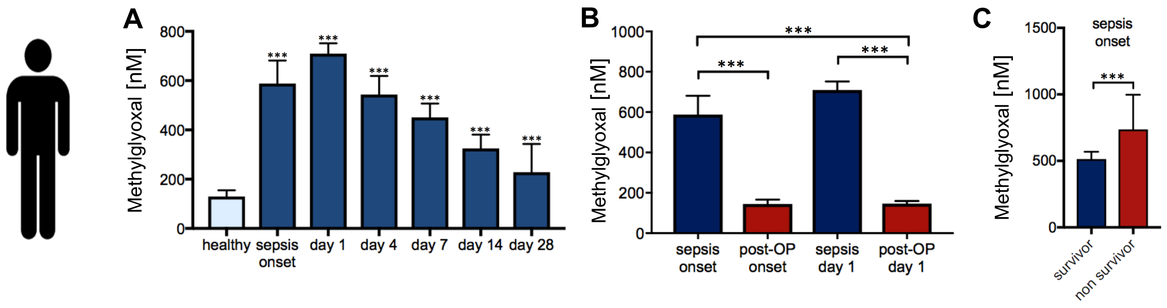
Background

1. The plasmatic load of MG and MG-AGE is associated with severe diabetic complications such as nephro-, retino- and neuropathy.
2. However, these late sequelae of DM develop within years.

<u>Remaining question:</u> Is MG able to evoke a pivotal influence on the course of the disease in sepsis within hours?

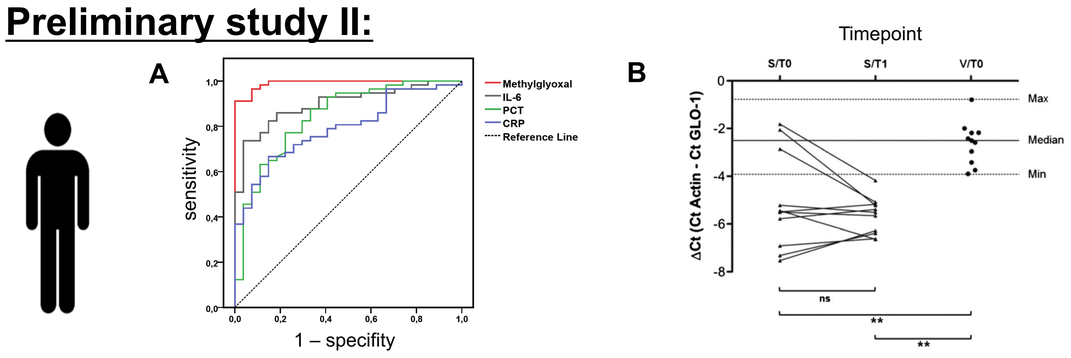
Background Data

<u>Preliminary study I:</u>



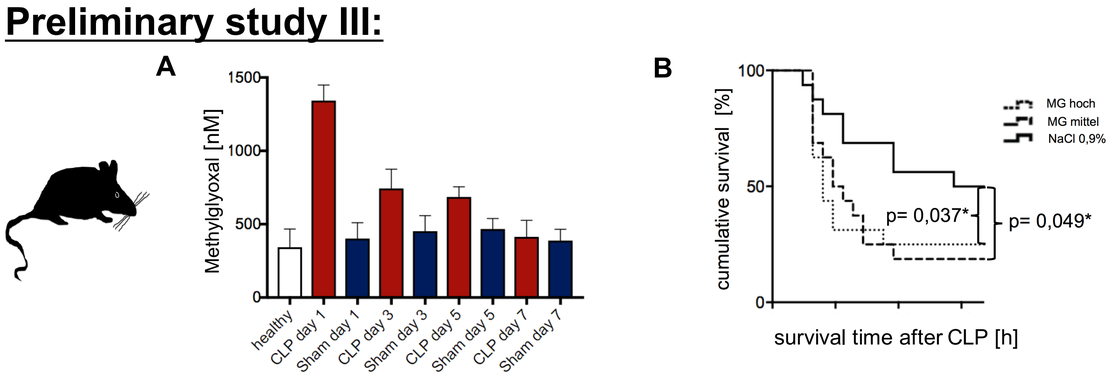
MG plasma levels are significantly increased in patients suffering from sepsis in comparison to healthy volunteers (A) and postoperative controls (B). At the time of sepsis diagnosis, non-survivors revealed significantly higher MG plasma levels in comparison to survivors (C).

<u>Preliminary study II:</u>



MG plasma levels proved to be superior for the identification of patients with sepsis as compared to the standard parameters PCT, IL-6 und CRP (A). Moreover, GLO-I expression in pBMCs of septic patients was shown to be significantly reduced in comparison to healthy controls (B).

<u>Preliminary study III:</u>

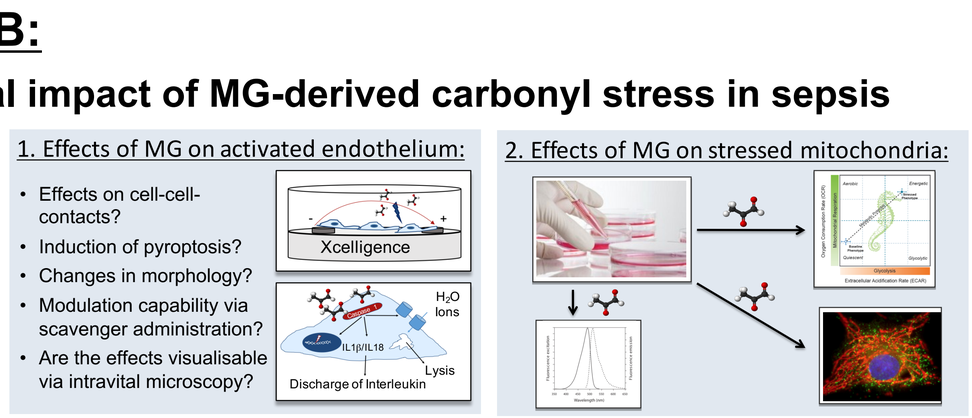


Plasma kinetics of MG in Cecal Ligation and Pucture (CLP)-induced murine sepsis were shown to be comparable to those of septic patients (A). Moreover, an additional MG-administration was associated with a dose-dependent decrease of survival in CLP-mice (B). Accordingly, MG-derived carbonyl stress might have a causal impact on the course of the disease in sepsis.

Work Program

<u>Aim A:</u>

Main source of MG-derived carbonyl stress in sepsis

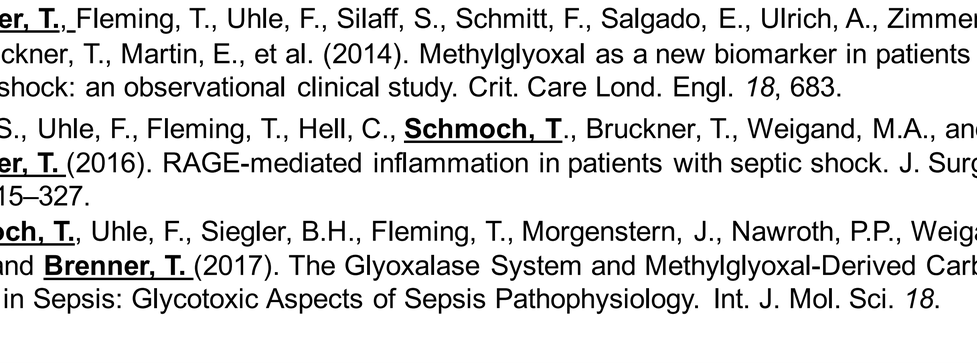


➡ **<u>Question:</u> Which cell entities show such an MG overload, which might serve as an explanation for the MG plasma kinetics observed in septic patients?**

Within the **1st step** we seek to investigate the relevance of exogenic (=bacterial) MG production in sepsis. Furthermore we will try to answer the question, whether a treatment with antibiotics is able to influence MG-derived carbonyl stress in sepsis. Afterwards we seek to identify the organs as well as the ensuing cell entities, which are responsible for MG-derived carbonyl stress in early sepsis (**2nd step**). Moreover, we will try to illuminate the underlying mechanisms for MG-accumulation in sepsis (**3rd step**: production↑ vs. **4th step**: detoxification↓).

<u>Aim B:</u>

Causal impact of MG-derived carbonyl stress in sepsis



➡ **<u>Question:</u> Via which mechanisms is MG able to influence the course of the disease in sepsis?**

A loss of the endothelial barrier is a decisive factor contributing to serious disturbances of microcirculation, ultimately leading to septic shock. Therefore, we first seek to investigate possible effects of MG-derived carbonyl stress on activated endothelium (**1st step**). Afterwards, we will try to evaluate the effects of MG on mitochondrial function as well as the global capacity of energy supply (**2nd step**).

Publications

➡ **<u>Brenner, T.</u>**, Fleming, T., Uhle, F., Silaff, S., Schmitt, F., Salgado, E., Ulrich, A., Zimmermann, S., Bruckner, T., Martin, E., et al. (2014). Methylglyoxal as a new biomarker in patients with septic shock: an observational clinical study. Crit. Care Lond. Engl. *18*, 683.

➡ Hofer, S., Uhle, F., Fleming, T., Hell, C., **<u>Schmoch, T</u>**., Bruckner, T., Weigand, M.A., and **<u>Brenner, T.</u>** (2016). RAGE-mediated inflammation in patients with septic shock. J. Surg. Res. *202*, 315–327.

➡ **<u>Schmoch, T.</u>**, Uhle, F., Siegler, B.H., Fleming, T., Morgenstern, J., Nawroth, P.P., Weigand, M.A., and **<u>Brenner, T.</u>** (2017). The Glyoxalase System and Methylglyoxal-Derived Carbonyl Stress in Sepsis: Glycotoxic Aspects of Sepsis Pathophysiology. Int. J. Mol. Sci. *18*.