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Intravital microscopic investigation of the effect of the selective alpha 7 nicotinic acetylcholine receptor agonist, GTS-21([3-(2,4- dimethoxybenzylidene)-anabaseine]), during endotoxemia in the mesenteric microcirculation

Fach-Einrichtung: Anästhesiologie
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BACKGROUND: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Microcirculatory alterations and endothelial dysfunction play a pivotal role in sepsis as a fundamental pathophysiology of multiple organs dysfunction. There is no effective therapeutic drug that can attenuate tissue edema formation due to increased endothelial dysfunction and microcirculation alterations in sepsis. Cholinergic anti-inflammatory pathway (CAP) has been shown to exert its anti-inflammatory effects through activation of the α 7 nicotinic ACh receptor (α7nAChR) that presents on macrophages and other immune cells during inflammation. GTS-21, a partial and selective α7nAChR agonist, could be an effective anti-inflammatory substance for sepsis-induced microvascular inflammation because of its cholinergic anti-inflammatory properties and its favorable safety profile in clinical trials.

AIM: The aim of this study was to evaluate the *in vivo* effect of GTS-21 on microvascular inflammation including microvascular permeability, leukocyte adhesion, and venular wall shear rate using an intravital microscopy (IVM) during experimental LPS-induced endotoxemia in rat model.

METHODS: To study the therapeutic effect of GTS-21 during endotoxemia, male Wistar rats (n=60) were randomly assigned into six groups receiving different treatments (n=10 for each group). The rats were anesthetized using sevoflurane inhalation combined with propofol (10 mg/kg) and fentanyl (5 μg/kg) for anesthesia induction and were maintained under anesthesia by continuous intravenous infusion of propofol (10-40 mg/kg/h) and fentanyl (10 μg/kg/h). During the 240 minutes observation time, the rat mesentery was prepared and evaluated for macromolecular leakage, leukocyte adhesion and venular wall shear rate in post-capillary

venules using IVM. Following baseline IVM recording, GTS-21 (1 mg/kg) was applied simultaneously with (co-treatment), 1 hour prior to (pre-treatment) and 1 hour after (post-treatment) administration of lipopolysaccharide (LPS, 5 mg/kg). Test substances (crystalloid solution, LPS, GTS-21) were administered as volume equivalent intravenous infusion over 5 minutes in the respective treatment groups. The sequential IVMs were performed at 60, 120 and 180 minutes after the baseline IVM. The systemic inflammatory response was evaluated by measuring TNF-α levels at baseline and after 180 minutes IVM.

RESULTS: Macromolecular leakage, was significantly decreased in animals treated with GTS-21 simultaneously (co-treatment) and 1 hour after administration of LPS (post-treatment). Leukocyte adhesion and venular wall shear rate in GTS-21 treatment groups were not significantly different compared to the untreated endotoxemic animals. In venular wall shear rate, a trend toward increasing velocity was seen in all GTS-21 treatment groups. TNF-α levels were not affected by GTS-21 treatment compared to the endotoxemia group.

CONCLUSION: GTS-21 significantly attenuated microvascular permeability indicating a protective effect on microvascular-endothelial barrier function during endotoxemia. This finding suggests a potential future role in the treatment of capillary leakage in sepsis therapy given its anti-inflammatory efficacy and pharmacologic safety profile.