REDUCED AUTOPHAGY CORRELATES WITH INCREASED APOPTOSIS IN THE KIDNEY OF BRAIN-DEAD RATS

Van Erp AC.[1] , Rebolledo R.[1,4], Ottens PJ.[1], Jochmans I. [2,3], Monbaliu D. [2,3], Pirenne J.[2,3], Leuvenink HGD.[1], and Decuypere JP.[2,3]

[1] Department of Surgery, University Medical Center Groningen, Groningen, The Netherlands, [2]Laboratory of Abdominal Transplantation, Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium, [3] Department of Abdominal Transplant Surgery, University Hospitals Leuven, Belgium, [4]Department of Surgery, Faculty of Medicine, University of Chile, Santiago, Chile

INTRODUCTION

Kidneys from brain dead donors have inferior outcome and higher rejection rates after transplantation compared to living donors. Brain death (BD) in the donor increases tissue injury and apoptosis. Apoptosis is generally counteracted by autophagy, a stress-adaptation protective catabolic pathway regulated by the mammalian target of rapamycin (mTOR). Dysregulation of autophagy has been linked to a number of diseases, such as ischemia/reperfusion-injury and sepsis, but whether it is affected by BD is unknown. This study investigates the dynamics of autophagy, apoptosis and tissue injury in the kidney of brain-dead rats.

AIMS

The effect of kidney autophagy to prevent from BD-induced renal injury is unknown. Therefore, we aimed to analyze the effects of BD on kidney autophagy and apoptosis in a male Lewis rat model subjected to 4 h of BD.

RESULTS

BD reduces kidney function

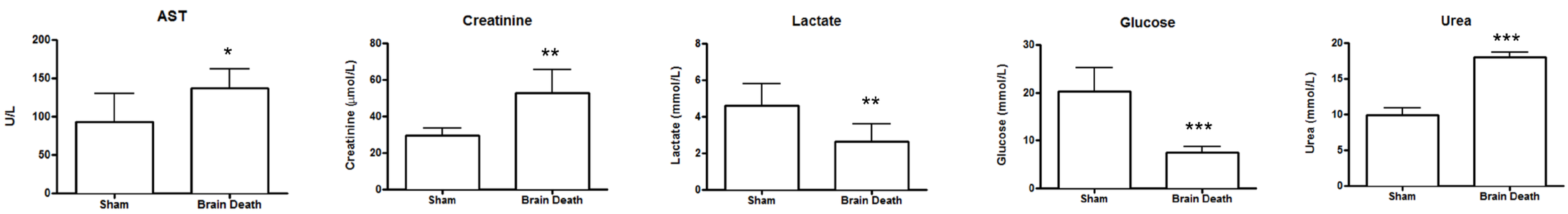

Fig. 1: Analysis of renal injury after 4 h of BD. Plasma was collected in male Lewis rats subjected to 4h of BD and analyzed for the assigned renal function markers. From left to right: aspartate aminotransferase (AST), Creatinine, Lactate, Glucose and Urea. (*N* = 7; * $p < 0.05$, ** $p < 0.01$,* $p < 0.001$; unpaired *t* test)**

BD reduces kidney autophagy and ir

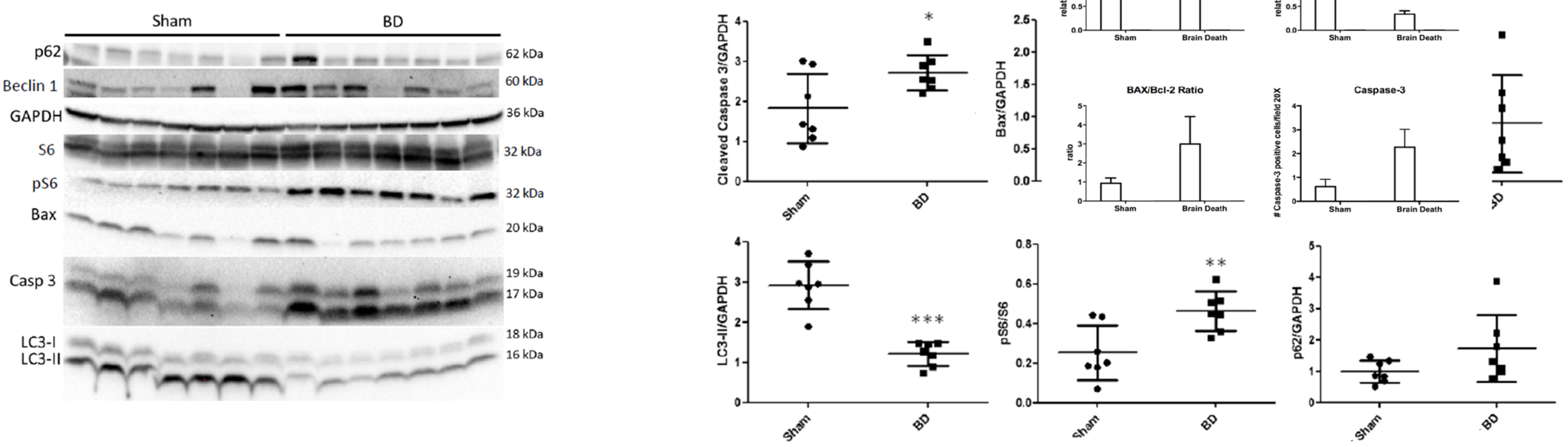

Fig. 2: Analysis of apoptosis and autophagy after 4 h of BD. Kidney tissues were collected in male Lewis rats sham-operated (Sham) or subjected to 4h of BD and analyzed for apoptosis (Bax, Cleaved Caspase 3), autophagy (LC3-II, p62, Beclin 1) and mTOR activity markers (phospho-S6). Right are the respective Western blots, left is the quantification of the seperate markers. (*N* = 7; * $p < 0.05$, ** $p < 0.01$,* $p < 0.001$; unpaired *t* test)**

Reduced autophagy correlates with increased apoptosis after BD

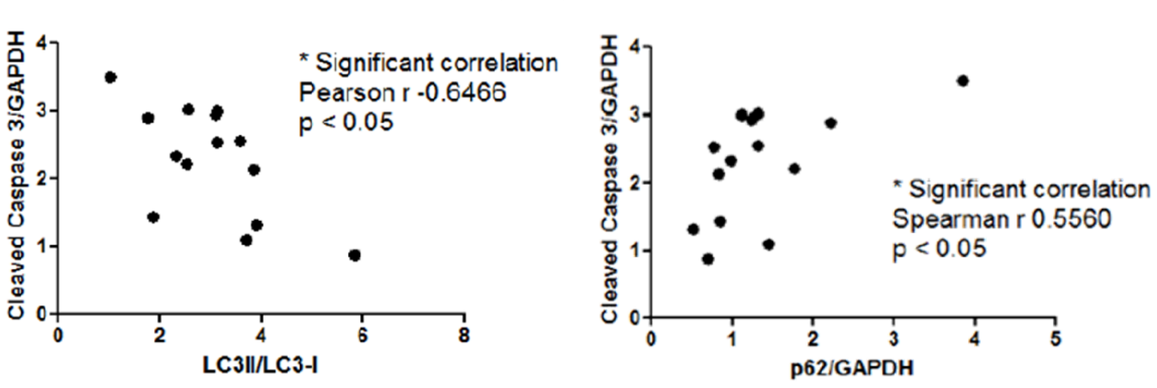

Fig. 3: Correlation between autophagy and apoptosis markers. In each sample, the values for autophagy LC3-II/LC3-I and p62/GAPDH were analyzed for correlation with apoptosis values Cleaved caspase 3/GAPDH. As LC3-II/LC3-I increased with autophagy, a significant negative correlation was found with Cleaved caspase 3/GAPDH. As p62/GAPDH decreases with autophagy, a significant positive correlation was found with Cleaved caspase 3/GAPDH. (*N* = 7; * $p < 0.05$)

Reduced Beclin 1 expression after BD

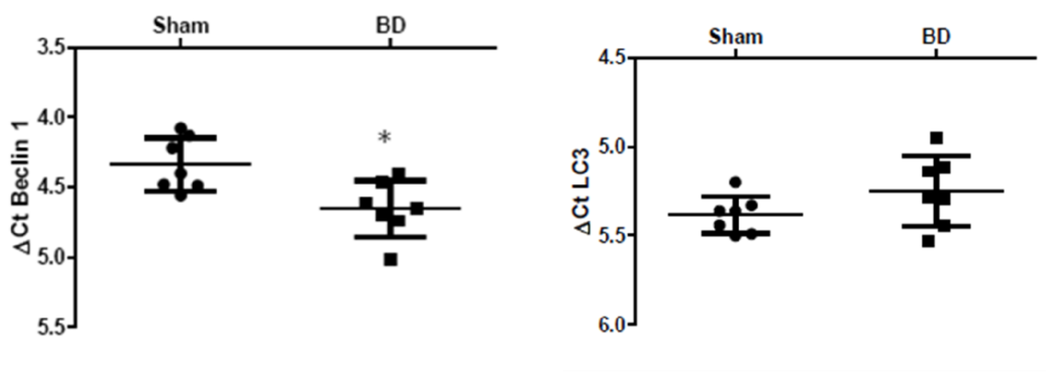

Fig. 4: qPCR analysis of autophagy markers Beclin 1 (left) and LC3 (right). Expression of Beclin 1 is significantly lower in the BD-subjected rats compared to Sham. (*N* = 7; * $p < 0.05$; unpaired *t* test)

CONCLUSIONS

1) Autophagy is reduced in the kidney after 4 h of BD, while apoptosis is increased
2) This is also reflected on the expression levels of Beclin 1, but not LC3
3) The reduction of autophagy significantly correlates with the increase in apoptosis, suggesting that increasing autophagy during BD could prevent from BD-induced apoptosis and perhaps renal injury.

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