BILASTINE PRESERVES THE GLOMERULAR JUNCTIONAL INTEGRITY IN A MURINE MODEL OF DIABETIC NEPHROPATHY

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Background and aim: In the last decades, compelling evidence suggest that an abnormal histamine-mediated intercellular signaling could contribute to the development of diabetic nephropathy (Pini et al., 2019and Grange et al., 2019). In particular, previous data point out at the histamine H1receptor as a possible pharmacological target to protect the glomerular dysfunction driven by hyperglycemia. Indeed, this receptor is expressed on podocyte cell membrane and its activation was related in vitro to the histamine-induced loss of podocyte adhesion proteins (Veglia et al., 2016). In parallel, (R)-cetirizine was demonstrated to reduce proteinuria and to increase Creatinine Clearance (CrCl) in diabetic rats (Anbar et al., 2016). However, these findings cannot be considered conclusive and further data need to be collected to better understand the pathophysiological and pharmacological role of H_1receptor in the context of diabetic nephropathy.

Methods: Diabetes was induced in DBA2/J male mice by multiple low-dose streptozotocin injection (50 mg/kg for 5consecutive days). From diabetes onset (glycaemia ≥200 mg/dl) mice received bilastine (1, 3, 10 and 30 mg/kg/day) by oral gavage for 14consecutive weeks. Weight gain and hyperglycemia were constantly monitored through the experimental period. Urine, blood and kidneys were collected at the end of the study. Urine function parameters, including urine volume, pH, proteinuria, albumin-to creatinine (ACR) ratio and CrCl were determined. Morphological analysis was performed by Periodic Shift staining (PAS) and electron microscope observation. Proinflammatory cells infiltration and renal fibrosis were assessed by hematoxylin/eosin and Picrosirius red staining, respectively. The expression of nephrin, synaptopodin, P-cadherin and podocin, proteins involved in the glomerular junctional integrity, was evaluated by immunoblotting.

Results: At the end of the experimental protocol diabetic mice showed polyuria (+195.5%), increase in ACR (+ 284.7%), and a significant drop in CrCl ($P < 0.05$). Bilastine prevented ACR increase and restored creatinine clearance in a dose-dependent manner, suggesting a positive effect on glomerular filtration. In parallel a beneficial effect on mesangial matrix expansion was observed for bilastine, irrespectively to the dose. The ultrastructural analysis showed a preserved junctional integrity. Consistently, animals treated with bilastine showed a preserved expression level of nephrin, synaptopodin and P-cadherin.

Conclusions: In conclusion, our data demonstrate that bilastine preserves the glomerular junctional integrity thus preventing the increase in ACR and the drop in CrCl. Therefore, these data further validate the hypothesis that H_1receptor could contribute to the glomerular damage occurring in diabetic nephropathy.