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EFFECT OF NCX 4016 OR ASPIRIN ON ENDOTHELIAL MODIFICATIONS OCCURRING IN DIABETIC RATS: A BIOCHEMICAL AND STRUCTURAL STUDY

M.V. Ambrosini [§], G. Mariucci [§], M.G. Rambotti [§], M. Tantucci [§], C. Passeri [§], G. Basta *, C. Covarelli [#], L. De Angelis [#], A. Monopoli [1], P. Del Soldato [1]
*[§]Dept. Exp. Med. & Biochem. Sci., *DIMISEM, University of Perugia, [#]Perugia General Hospital, Perugia, Italy; [1]NicOx Research Institute, Milano, Italy*

Several diseases, including diabetes mellitus, are associated with and exacerbate by micro- and macrovascular complications due to endothelial dysfunction. As a consequence, such patients have elevated risk of myocardial infarction and stroke, mostly releated to an increased platelet adhesiveness and aggregation (Vane, 1990; Nathan 1993). It is assepted the treatment with aspirin (ASA) to prevent platelet adhesiveness and aggregation (Fitzgerald 1983). It has recently been proposed that hyperglycemia has a pivotal role in both the initiation and maintenance of endothelial dysfunction via a reduced availability of NO (Goligorsky, 2000). In particular, endothelial dysfunction seems to be primed by the ability of elevated levels of glucose to scavenge NO. According to this, diabetic complications may be prevented or reduced by maintaining NO bioavailability close to the physiological levels (Goligorsky, 2000). In this study we examined the effect of both NCX 4016, a nitric oxide (NO) releasing aspirin derivative, and aspirin (ASA) treatment on aortic endothelium of diabetic rats by using scanning and transmission electron microscopy (SEM and TEM, respectively).
Methods. The study was conducted in young adult male Wistar rats (n= 78, 165-190 g; Harlan Italy). Diabetes was induced by streptozotocin (65 mg/kg i.p.). One week after injection, diabetic rats (glucose 200-600 mg/dl) were randomly divided into 4 groups: NCX 4016 100 mg/kg (n=12), ASA 54 mg/kg (n=12), Vehicle (n=12) and diabetic controls (DC, n=12). Non-diabetic (ND) control rats were also studied. The drugs were given daily for 6 weeks by oral administration. Metabolic control was assessed by measuring blood and urine metabolites, and 24-h urine volume. Immediately after the sacrifice, the thoracic aorta was removed and quickly processed for SEM and TEM study.
Results. STZ treatment induced a persistent increase in blood glucose which was not influenced by pharmacological treatments. Values of blood metabolites were in line with the diabetic status. Interestingly, the BUN values increased in DC, Vehicle and ASA groups, whereas they were normal in NCX 4016 rats. Moreover, creatinine clearance tended to decrease in NTD, Vehicle and ASA groups, whereas it was normal in NCX 4016 rats. SEM study of aortic endothelium showed: i) many and widespread pathological signs in DC, Vehicle and ASA groups; ii) scanty and scattered pathological findings in ND and NCX 4016 rats. TEM study of aortic endothelium confirmed the results obtained by SEM.
Our data document the protective effects of NCX 4016 on macrovascular endothelium of diabetic rats and, possibly, on kidney function. In fact, NCX 4016 protected endothelial structure and did not change blood urea values. Since ASA had no protective action, possibly NCX 4016 exerted its beneficial action by releasing NO.

References
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