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BIOCHEMICAL BASIS FOR BLADDER DYSFUNCTION IN EXPERIMENTAL DIABETES: GLYCOXIDATIVE AND OXOALDEHYDE STRESS ARE MARKEDLY ENHANCED IN SOLUBLE AND INSOLUBLE BLADDER PROTEINS

Hypothesis / aims of study

Bladder dysfunction is a major cause of disabilities in diabetes mellitus. Alterations in the tissue and functional characteristics of the detrusor muscle may play a major role in such dysfunction. Here we have investigated the formation of glycation and advanced glycation products in the modification of soluble and insoluble fractions proteins from streptozotocin-diabetic and control rats.

Study design, materials and methods

After ICAC approval, diabetes was induced in male Sprague-Dawley rats by a single intraperitoneal injection of STZ (60 mg/kg) dissolved in citrate buffer. By design, the rats were allowed to live 12 weeks after establishment of diabetes (n=6). After induction of anesthesia by urethane (1.2 g/kg, s.c.), cystometrogram (CMG) was conducted via a suprapubic catheter. After completion of CMG, the bladder was removed and weighed. Bladder tissue was minced, homogenized and separated into soluble predominantly cytoplasmic and insoluble proteins. Furosine (glycated lysine), carboxymethyl-lysine (CML), carboxyethyl-lysine (CEL) and pentosidine were determined as trimethylsilyl derivatives by chromatography/mass spectrometry in the acid hydrolyzate.

Results

At 12 weeks mean bladder weight was significantly increased in diabetic vs. control rats ($p<0.01$). The cystometry showed an increased compliance and capacity in diabetic rats ($p<0.001$). Furosine, a marker of glucose concentration, and CML, a glycoxidation product, were increased 220 – 250% in both soluble and insoluble fractions from diabetic rats ($p< 0.001$). Insoluble proteins were 5-6 fold more modified than soluble ones ($p<0.001$). CEL, a marker of methylglyoxal levels, was 176% ($p<0.001$) and 167% ($p<0.01$) increased in soluble and insoluble fractions respectively. However, in contrast to furosine and CML, CEL levels were higher in the soluble than the insoluble fraction ($p<0.01$, and <0.001, respectively). Pentosidine, another glycoxidation marker was also elevated in the insoluble protein fraction ($p< 0.05$).

Interpretation of results

All major AGEs including CML, CEL, Furosine and Pentosidine are elevated in the detrusor muscle of diabetic rat.

Concluding message

These data provide the first evidence for a broad increase in carbonyl stress to bladder proteins in experimental diabetes, which may in part participate in bladder dysfunction by impairing protein function.

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