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DIABETIC BLADDER DYSFUNCTION IS ALTERED BY OBESITY

Hypothesis / aims of study
Although diabetic bladder dysfunction (DBD) is a frequent complication that affects nearly 80% of diabetic patients, the causes involved in the development of DBD remain elusive, particularly when compounded by urologic consequences of obesity. These frequently comorbid conditions are each characterized by insulin resistance and hyperglycemia. Most animal models of type 2 diabetes are also obese, confounding the identification of distinct effects of each of these diseases on detrusor function. Previous studies showed that the genetic deletion of insulin receptor substrates 1 and 2 in mice causes insulin resistance and hyperglycemia without development of obesity. These double knockout (DKO) mice develop a temporal pattern of dysfunction that parallels the features of DBD observed in humans. Thus, DKO mice could represent an ideal animal model to investigate DBD independently from obesity induced bladder dysfunction. The purpose of this study was to investigate the impact of obesity on DBD in diabetic mice fed a high fat diet (HFD).

Study design, materials and methods
Female 12-14 week old DKO mice and age matched control WT mice were fed for ten weeks with high fat diet (DKO+HFD and WT+HFD respectively). These animals were compared with age matched DKO and WT mice that were fed standard chow for the same period of time. Fasting glucose levels and body weights were monitored in each group. At the end of ten weeks, urinary bladders were harvested from each animal and functionally tested by *ex vivo* isometric tension studies. In half of the muscle strips, the mucosa was removed. Detrusor contractions induced by administration of α-β-methylene ATP (αβmeATP, 10μM), carbachol (CCh, 1nM-10μM), KCl (120mM), or electrical field stimulation (EFS, 40V, 1-64Hz) were measured in both intact and mucosa-denuded strips, and the amplitude of responses compared among groups.

Results
HFD caused hyperglycemia in WT mice and increased glucose levels further in hyperglycemic DKO mice compared with normal diet DKO. In addition, HFD significantly increased the body weight of both DKO and WT mice, with WT+HFD having the highest body mass. On normal diet, contractile responses induced by αβmeATP, CCh, and EFS were significantly higher in DKO bladders compared to WT in tissue with or without mucosa. In bladder tissue with intact mucosa from DKO+HFD, the amplitude of contractions in response to agonists and EFS were not significantly different from those obtained in DKO fed normal diet. However, in tissue without mucosa from DKO+HFD, contractile responses induced by CCh, KCl and EFS were significantly higher than the responses from DKO fed standard chow. In contrast, agonist and KCl induced contractions from WT tissue were not significantly affected by HFD. However, HFD significantly augmented the amplitude of EFS induced contraction compared to WT fed with normal diet.

Interpretation of results
Compared to WT, the augmented contractile responses to both nerve-mediated and agonist-induced stimulation observed in DKO bladders reflect the compensated phase occurring in the early stage of diabetic bladder dysfunction in these animals. HFD appeared to have a more pronounced impact in diabetic bladders than in WT. Differences in the effect of HFD on contractile responses in DKO bladder tissue with and without mucosa indicate that both smooth muscle and mucosal compartments become altered by HFD in diabetes.

Concluding message
These findings suggest that obesity alone may alter neurotransmission, but in the setting of diabetes, obesity differentially affects smooth muscle and mucosal contributions to bladder contractile function. Furthermore, DKO mice provide a useful animal model to investigate the independent effects of diabetes and obesity on bladder function.

Disclosures
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