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ATTENUATION OF BLADDER OVERACTIVITY IN KIT (WS /WS) MUTANT RATS

Hypothesis / aims of study

The interstitial cells of Cajal (ICC) are primary pacemaker cells responsible for generating smooth muscle activity in the gastrointestinal tract. ICCs express the proto-oncogene c-kit, 3 and signaling via the receptor kinase gene product, KIT, is essential for the development of phenotype and rhythmicity. ICC-like cells form close connections with suburothelial nerves by gap junctions, supposedly involved in signaling pathways of the bladder, and may play a role in moderating the sensory process and lead to initiation of the micturition reflex. Although KIT is used as an identification marker of ICCs and ICC-like cells, recent reports have suggested that KIT is not only a detection marker of these cells, but also may play a crucial role in the control of bladder function. In the present study, to clarify whether disturbance of the KIT pathways affects bladder activity, we examined morphological and physiological findings in the bladder of KIT mutant rats to identify the role of KIT in the control of bladder function, and discussed the potential role of KIT-positive ICC-like cells in the urinary bladder.

Study design, materials and methods

The homozygous KIT mutant (WsRCWs/Ws) rats and wild-type (WsRC+/+) rats were used in this study. The Ws mutant locus shows a deletion of bases at the tyrosine kinase domain of c-kit. First, we performed RT-PCR to confirm the expression of c-kit mRNA in the bladder of these rats. Second, we used light and transmission electron microscopy to identify morphological and ultrastructural characteristics of the ICC-like cells of KIT mutant rats. Third, we used bladder-filling cystometry to examine the voiding pattern of KIT mutant rats and the effects of cyclophosphamide (CYP) and protamine sulfate (PS) on bladder function.

Results

In wild-type rats, c-kit mRNA expression was observed in the urinary bladder, while it was not detectable in KIT mutant rats. ICC-like cells of KIT mutant rats were intact and morphologically indistinguishable from those of wild-type rats. In control rats (WsRC+/+control and WsRCWs/Ws control), there was no significant change in each parameter of cystometry between rats with and without KIT mutation. In the wild type with CYP-induced cystitis (WsRC+/+CYP), there were changes in the parameters of cystometry, that is, shortening of the intercontraction interval (264.0+/-105.2 second) compared with control rats (430.6+/-65.1 second; WsRC+/+ control vs WsRC+/+CYP, $P<0.01$). Interestingly, these significant changes were not observed in WsRC Ws/Ws rats in spite of CYP treatment (WsRCWs/WsCYP; 512.1+/-198.6 second). There were significant differences in the intercontraction interval between WsRC+/+CYP and WsRCWs/WsCYP ($P<0.05$), while there was no significant differences between the WsRCWs/Ws control (457.0+/-69.9 second) and WsRCWs/WsCYP. There was no significant difference in other parameters, including maximal voiding pressure, pressure threshold and baseline pressure, between WsRC+/+CYP and WsRCWs/WsCYP rats. The intercontraction interval was shorter in PS instillation rats according to PS concentration than in saline instillation rats; however, the degree of shortening of the intercontraction interval was smaller in WsRCWs/Ws rats than in WsRC+/+ rats significantly in two PS concentrations groups (1mg/ml, 2mg/ml; respectively, $P<0.05$).

Interpretation of results

Our data suggest that attenuation or disturbance of KIT activity in ICC-like cells of KIT mutant rats bladder may demonstrate the possibility of negatively regulating the sensory pathway of bladder hyperactivity mediated by C-fibers, and therefore, the KIT pathway modulates the sensitivity of bladder afferent nerves.

Concluding message

Certain voiding disturbances may be associated with impaired KIT signaling in ICC-like cells and the KIT-signaling pathway might have a significant role in the pathogenesis of DO. KIT could be a candidate target of medical therapy in the future.

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