Retigabine induces relaxations of the human bladder detrusor

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Retigabine is an anticonvulsant drug indicated as adjunctive treatment of partial onset seizures in adults. It exerts its anticonvulsant action by reducing neuronal excitability through activation of type 7 voltage-dependent K^+ (K_V7) channels encoded by the KCNQ genes (Rundfeldt et al., 2000). These channels include 5 subtypes ($K_V7.1$-7.5) and play important roles in regulating the membrane potential of various cell types, including cardiomyocytes and neurons (by activating $K_V7.1$ homomers and $K_V7.2/7.3$ and $K_V7.3/7.5$ heteromers, respectively) (Soldovieri et al., 2011). K_V7 channels also regulate smooth muscle activity in different systems (Greenwood and Ohya, 2009). The aim of the present study was to investigate the motor effects of retigabine in the human bladder detrusor. Specimens of detrusor were obtained from patients undergoing radical cystectomy for bladder cancer. The study was approved by the local Ethics Committee and all patients signed an informed consent. Muscle strips prepared from the detrusor were suspended under isotonic conditions (9.8-mN load) in Krebs solution maintained at 37° C and bubbled with carbogen inside 5-ml organ baths. Retigabine (1-100 μM) induced concentration-dependent relaxations of bethanechol (5 μM)-precontracted strips. The maximal relaxation induced by retigabine (100 μM) was 51.8±5.3 % of bethanechol-produced precontraction (n=6). DMSO, the solvent in which retigabine was dissolved, at the maximal concentration used (0.5 %) relaxed bethanechol-precontracted strips by 17.5±0.9 % (n=4, $P<0.05$ vs. retigabine). The K_V7 blocker XE-991 (20 μM) (Wang et al., 1998) reduced retigabine (100 μM)-induced relaxation to levels very close to those produced by DMSO (47.0±5.6 % and 20.8±9.0 % of bethanechol-produced precontraction without and with XE-991, n=4, $P<0.01$). The relaxation produced by retigabine (100 μM) was not significantly affected by tetrodotoxin (1 μM) and ω-conotoxin GVIA (30 nM) (104.5±13.1 % and 109.3±2.5 % of controls, respectively, n=3 each). Our results indicate that the activation of muscular K_V7 channels produces significant relaxations of the human bladder detrusor, suggesting that these channels could be considered as pharmacological targets for the treatment of urinary bladder motor disturbances.

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