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**Oxytocin blocks IKs and IK1 - thus exerting harmful cardiac repolarization prolonging effects particularly in context of drug-induced LQTS**

**Authors:**
P Kreifels¹, I Bodi¹, G Franke¹, S Perez-Feliz¹, A Castiglione¹, D Ziupa¹, M Brunner¹, C Bode¹, KE Odening¹, University of Freiburg, University Heart Center Freiburg, Department of Cardiology and Angiology 1 - Freiburg - Germany,

**Topic(s):**
Vascular Biology and Physiology: Ion Channels, Electrophysiology

**Citation:**

Introduction: Oxytocin, is used therapeutically in patients with autism or borderline disorders. Many of these patients receive anti-depressant and/or anti-psychotic drugs, which cause acquired long QT 2 (LQT2) by blocking IKr. We have previously identified a QT-prolonging effect of oxytocin in transgenic LQT2 rabbits due to an oxytocin-induced reduction of IKs.

Purpose: We aimed at elucidating whether a combination of the two therapeutic strategies may be harmful due to severe QT prolongation and pro-arrhythmia.

Methods: Adult female wildtype rabbits were subjected to in vivo12-lead ECGs 1) at baseline, 2) during perfusion with risperidone (risp, 0.3mg/kg bolus, followed by 3mg/h iv; alone and with oxytocin, oxy 6U/h iv, n=21) or 3) with fluoxetine (fluo, 1 mg/kg bolus, followed by 9 mg/h iv; alone and with oxy, n=23) and 4) oxytocin alone (oxy, 1, 5 U bolus, followed by 6U/h iv, n=13). Ex vivomonophasic action potentials were measured in Langendorff-perfused rabbit hearts and patch clamping experiments were performed in isolated cardiomyocytes exposed to oxy (200ng/l, n=8), risp (1µM, n=8) or fluo (3µM, n=10) alone and with oxy (200ng/l).

Results: Oxytocin as well as fluo and fluo+oxy prolonged QTc compared to baseline (ms, bsl, 251.1±4.8 vs. oxy, 262.5±5.6; p<0.001, 244.1±2.4 vs. fluo, 259.0±3.1 vs. fluo+oxy 267.5±3.5; p<0.0001). The fluo+oxy combination showed an additional QTc-prolonging effect (p<0.001). Similar effects were found for risp and risp+oxy (ms, bsl, 248.3±2.1 vs. risp, 288.7±3.9 vs. risp+oxy 296.4±4.3; p<0.0001).

Oxy prolonged mean action potential duration (APD75, ms, bsl, 127.1±7.6 vs. oxy, 136.3±10.1, n=8, p=0.05). Fluo+oxy prolonged APD75compared to baseline (bsl, 120.6±4.4ms vs. fluo+oxy, 140.2±2.8ms; p<0.001) and the combination fluo+oxy further increased APD (ms, fluo, 129.9±5.0 vs. fluo+oxy, 140.2±2.8, p<0.05) with similar results found for risp and risp+oxy (ms, bsl, 122.5±3.9 vs. risp, 149.2±6.3 vs. risp+oxy, 152.9±5.9; p<0.01). Similar APD prolonging effects were observed in isolated cardiomyocytes (p<0.05). This is due to differential effects of oxy, risp and fluo on repolarizing ion currents: Oxy reduced IKs, while both fluo and risp reduced IKr, resulting in additive effects on IKtotal-tail (+40mV, % reduction of pA/pF, oxy -35% (n=12), 'fluo -67% (n=17), fluo+oxy -72% (n=10); risp -55% (n=10), risp+oxy -75% (n=7)). In addition, oxy reduced IK1(-120mV pA/pF, bsl, -35.4±3.7 vs. oxy, -29.9±2.6, n=11, p<0.05) thus further reducing the repolarization reserve in cardiomyocytes while risp and fluo alone had no effects on IK1.

Conclusion: Oxytocine, risperidone and fluoxetine prolong QTc and APD. Combined treatment with fluo+oxy further prolongs QTc and APD due to differential effects of oxy and risp / fluo on IKsand IK1(block by oxy) and IKr(block by risp and fluo) leading to pronounced impairment of repolarization reserve. Oxytocin should therefore be used with caution in the context of acquired LQTS.
Abstract: Oxytocin blocks IKs and IK1—thus exerting harmful cardiac repolarization prolonging effects particularly in context of drug-induced LQTS.

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