

Figure S1. Insulin secretion and content upon treatment with bisphenols. (A and B) Insulin secretion was measured at 2.8, 8.3 and 16.7 mM glucose in islets from C57BL/6J mice treated *ex vivo* with vehicle (control; black circles and white bars) or 1 nM BPA (red circles and light grey bars). (A) After 2 h of recovery, treatments (vehicle or BPA) were added to each glucose solution so that the islets remained under treatment during the whole experiment. (B) Islets were treated *ex vivo* with vehicle or BPA for 48 h, and then, glucose-stimulated insulin secretion was performed in the absence of treatments. (C-H) Insulin content was measured after GSIS of the experiments described in the **Figure 1**. Mouse islets from C57BL/6J mice treated *ex vivo* with vehicle (control; black circles and white bars), 1 nM BPA (A and F; red circles), BPS (D and G; green circles) or BPF (E and H; yellow circles). Insulin content was measured by ELISA. Data are shown as means \pm SEM of six independent islet preparations isolated on three different days: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs 2.8 mM; # $p \leq 0.05$, ## $p \leq 0.01$, ### $p \leq 0.001$ comparisons indicated by bars (one-way ANOVA); & $p \leq 0.05$ (Student's t-test).

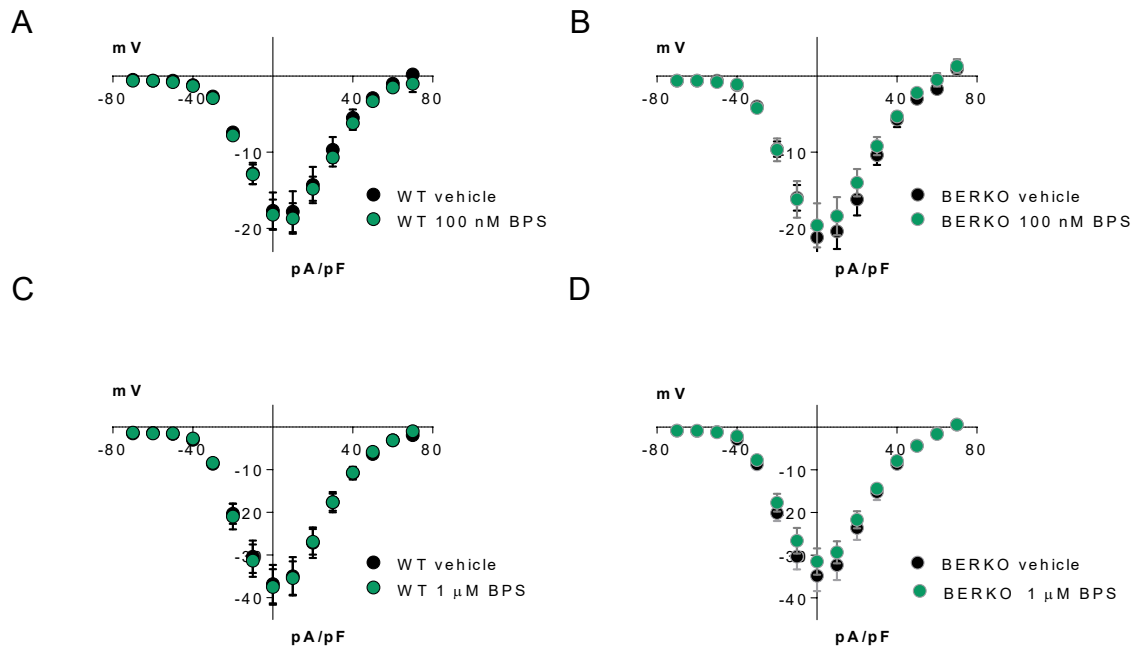


Figure S2. 100 nM and 1 μ M BPS do not reduce whole-cell Ca^{2+} currents via $\text{ER}\beta$ in β -cells. (A and B) Average relationship between Ca^{2+} current density (Ca^{2+} currents in pA normalized to the cell capacitance in pF) and the voltage of the pulses in wild-type (WT, A and C) and BERKO (B and D) control cells (black circles) and cells treated (green circles) with 100 nM BPS (A and B) or 1 μ M BPS (C and D). The effect of BPS was measured after 48 h of incubation. The methodology for patch-clamp recordings of voltage-gated Ca^{2+} currents is the same as the one described in Figure 4. Data are shown as means \pm SEM of the number of cells recorded in WT (n=10-15 cells) and BERKO (n=7-15 cells) mice. These cells were isolated from six mice on at least three different days: * $p \leq 0.05$ vs control (one-way ANOVA).

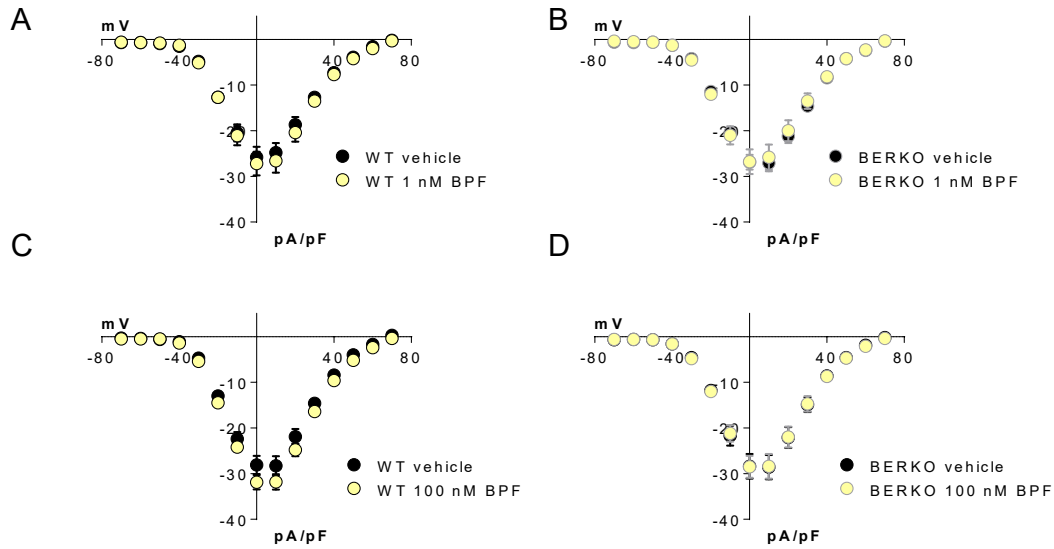


Figure S3. 1 nM and 100 nM of BPF do not reduce whole-cell Ca²⁺ currents via ERβ in β-cells. (A and B) Average relationship between Ca²⁺ current density (Ca²⁺ currents in pA normalized to the cell capacitance in pF) and the voltage of the pulses in wild-type (WT, A and C) and BERKO (B and D) control cells (black circles) and cells treated (yellow circles) with 1 nM BPF (A and B) or 100 nM BPF (C and D). The effect of BPF was measured after 48 h of incubation. The methodology for patch-clamp recordings of voltage-gated Ca²⁺ currents is the same as the one described in Figure 4. Data are shown as means ± SEM of the number of cells recorded in WT (n=13-21 cells) and BERKO (n=9-23 cells) mice. These cells were isolated from six mice on at least three different days: *p<0.05 vs control (one-way ANOVA).

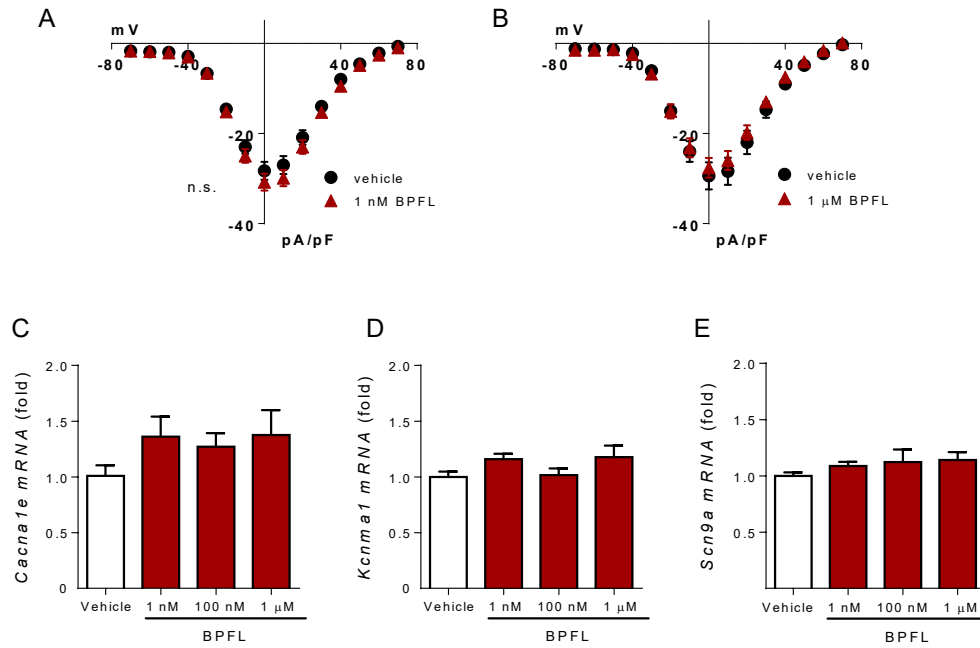


Figure S4. Bisphenol FL does not change whole-cell Ca²⁺ currents or *Cacna1e*, *Kcnma1* and *Scn9a* mRNA expression in mouse islets. (A and B) Average relationship between Ca²⁺ current density (Ca²⁺ currents in pA normalized to the cell capacitance in pF) and the voltage of the pulses (-60 to +70 mv from a holding potential of -70 mV, 50 ms duration) in isolated β-cells treated *in vitro* with vehicle (black circles) or with 1 nM BPFL (A; red triangles) or 1 μM BPFL (B; red triangles). The effect of BPFL was measured after 48 h of incubation. Data are shown as means ± SEM of the number of cells recorded in vehicle (n=8-10 cells) and BPFL (n=7-9 cells). These cells were isolated from six mice on at least three different days (C-E) mRNA expression of *Cacna1e* (C), *Kcnma1* (D) and *Scn9a* (E) was measured in islets from C57BL/6J mice treated *ex vivo* with vehicle (white bars) or BPFL (red bars) at 1 nM, 100 nM, and 1 μM for 48 h. mRNA expression was measured by qRT-PCR and normalized to the housekeeping gene *Hprt1*, and is shown as fold vs. mean of the controls. Data are shown as means ± SEM of: four to twenty independent samples from up to twenty islets preparations isolated on at least three different days (one-way ANOVA).

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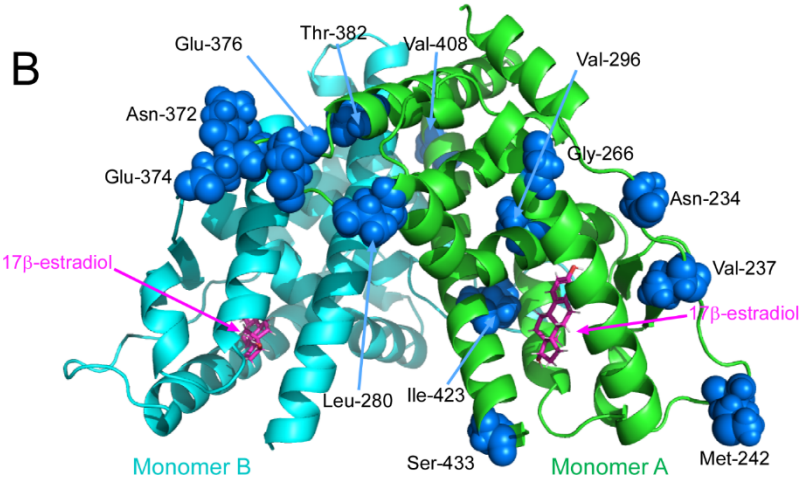


Figure S5. Sequence alignment of human, rat and mouse LBD-ER β . (A) Multiple sequence alignment of human, rat and mouse ER β . A yellow box indicates the region of the protein corresponding to the LBD and whose structure has been resolved from x-ray diffraction data. An orange box locates the human Cys-339 that can be palmitoylated. (B) Secondary structure of the rat ER β -LBD dimer (PDB ID 1HJ1) that includes a 17 β -estradiol molecule in the ligand-binding cavity of each subunit. Monomer A (green) highlights the different amino acids (spheres, Asn-234, Val-237, Met-242, Gly-266, Leu-280, Val-296, Ala-369, Ser-370, Asn-372, Glu-374, Glu-376, Thr-382, Val-408, Ile-423, Ser-433) in the human isoform.

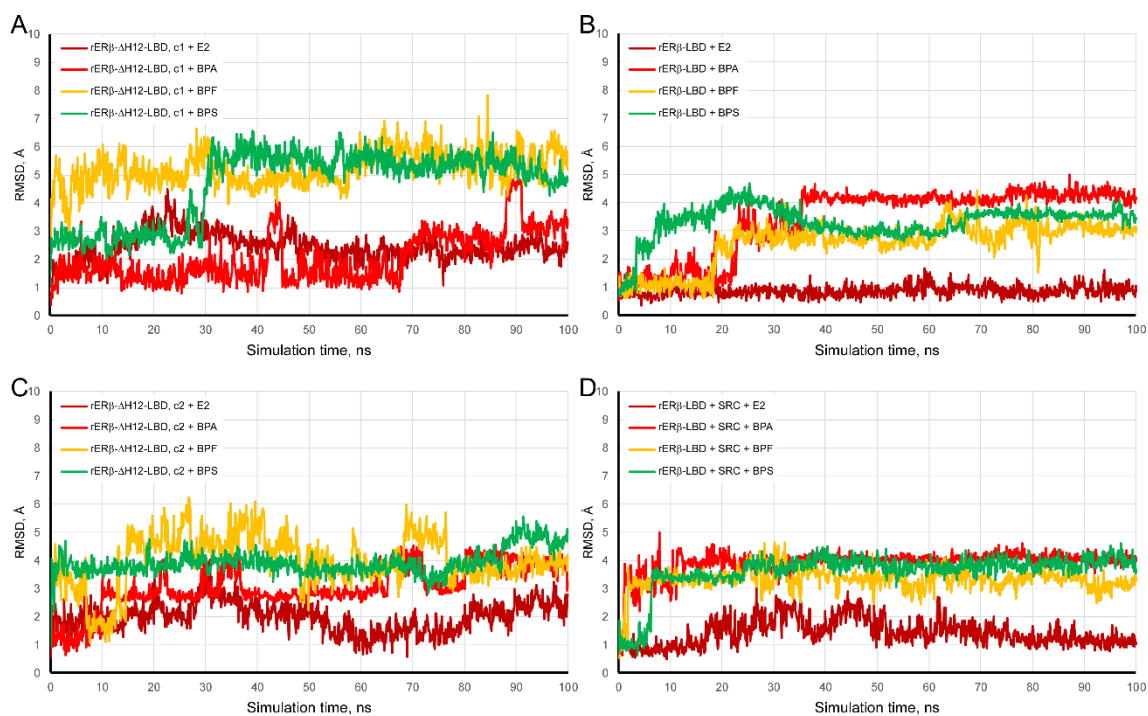


Figure S6. Analysis of trajectories for molecular dynamics simulations of LBD-ER in complex with different ligands. **A** and **C** Trajectories (RMSD, Å) of the different ligands initially docked to the main cavity of the open rER β - Δ H12-LBD dimer. Cavity 1 (c1, **A**) and cavity 2 (c2, **C**). **B** and **D** Trajectories (RMSD, Å) of the different ligands docked to the closed cavity of the rER β -LBD monomer in the absence (**B**) or presence (**D**) of the SRC co-activating peptide, respectively. The legends included within each panel indicate the different ligands analyzed.

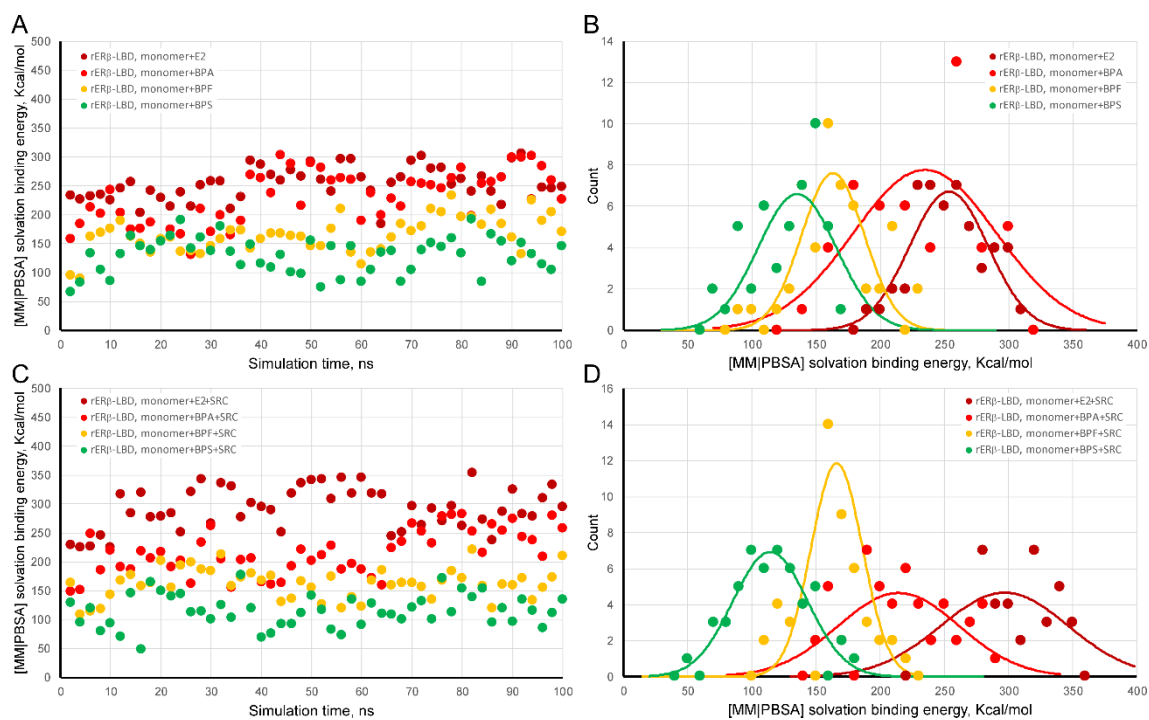


Figure S7. Calculated MM/PBSA solvation binding energy for bound E2 and bisphenols to the H12 closed rER β -LBD alone or in the presence of the Src peptide. (A and C) Calculated MM/PBSA solvation binding energy values of each ligand attached to LBD cavity alone (A) or in the presence of the Src peptide (C). (B and D) Frequency distributions of the values shown in (A) and (C), respectively. A Gaussian curve overlaps discrete data. The legends included within each panel indicate the different ligands analyzed.