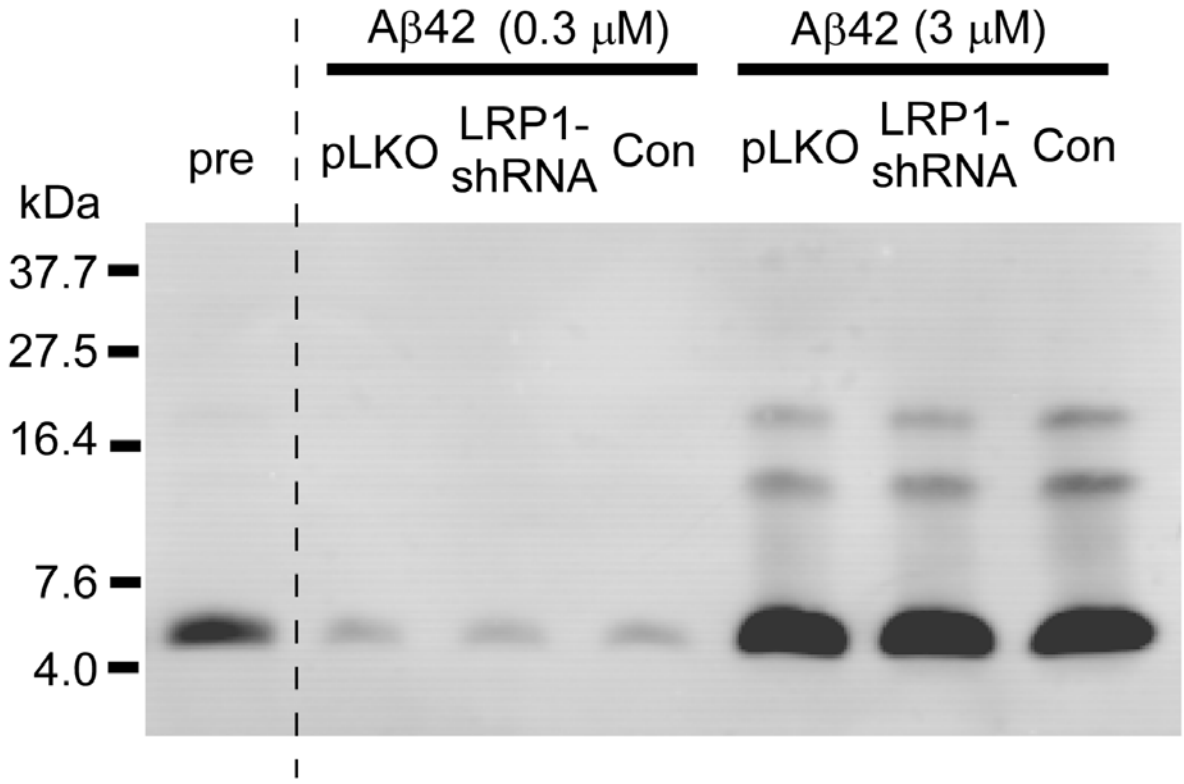

Figure S1. Aβ42 in the conditioned media of primary neuron cultures. Neurons were infected with pLKO or LRP1-shRNA lentiviruses for three days. Thereafter, infected neurons and non-infected, control neurons were incubated with Aβ42 (0.3 μM or 3 μM) for 24 h and the aggregation states of Aβ42 in the conditioned media were analyzed by Western blot. A freshly resuspended aliquot of Aβ42 was used as a control for assessing the monomeric nature of the starting material (pre, 1 μM). Approximately 10% of Aβ42 was changed to SDS-stable oligomers under our experimental conditions.

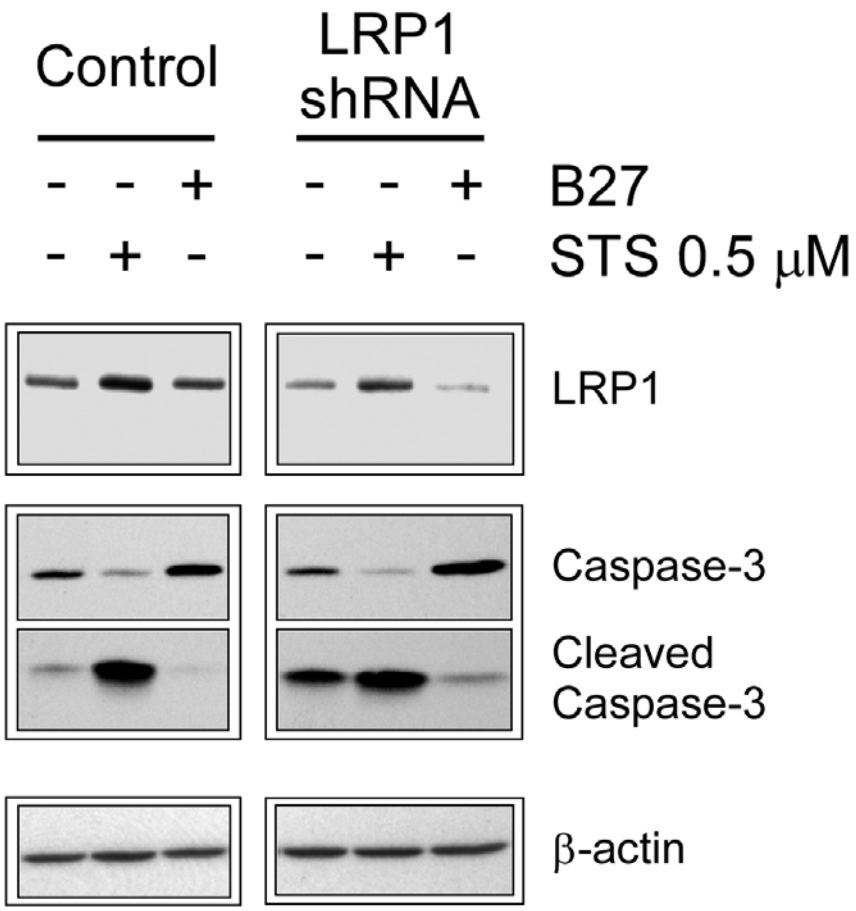

Figure S2. LRP1 knockdown leads to increased caspase-3 activation in staurosporine-treated neurons. Primary neurons were infected with control or LRP1 shRNA and LRP1, full-length caspase-3, cleaved caspase-3 and β-actin levels were analyzed by Western blot upon 18 h treatment with 0.5 μM staurosporine.

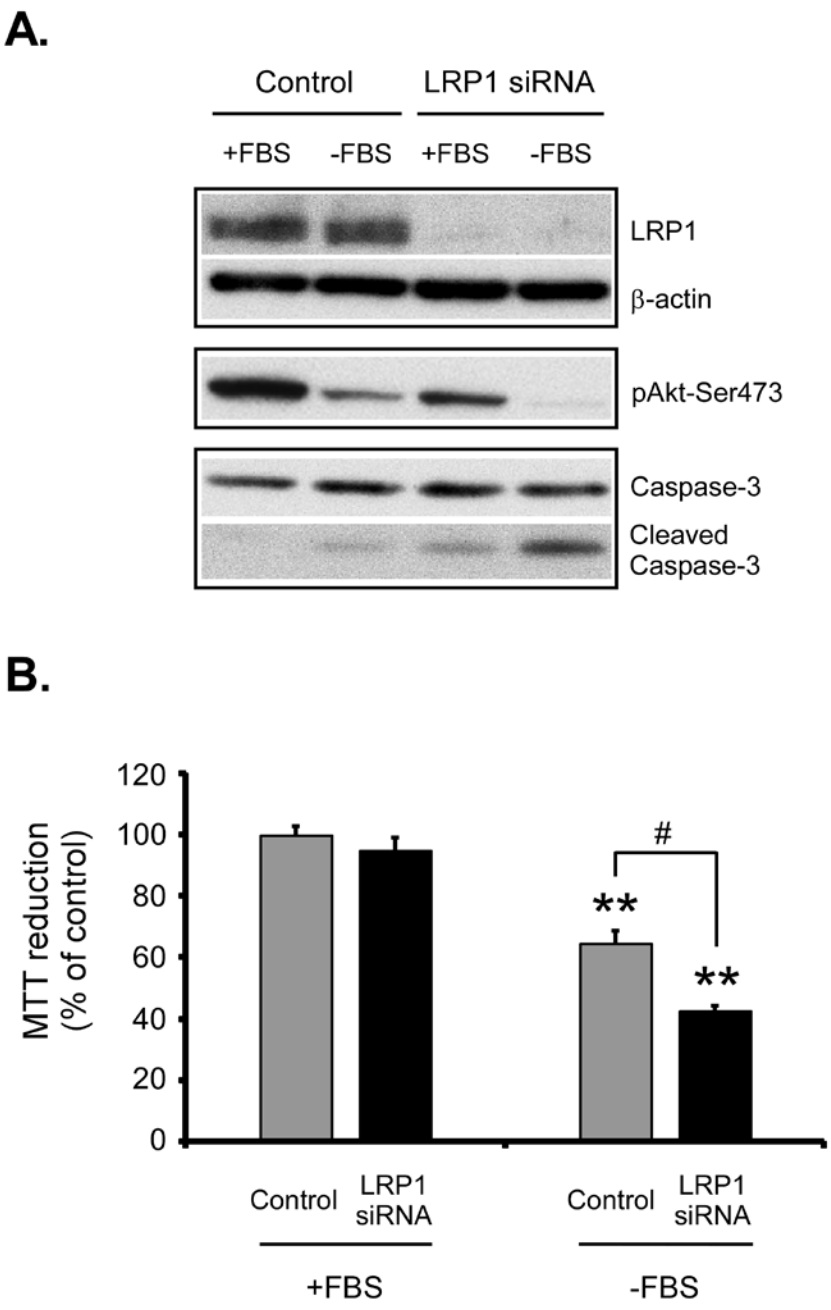

Figure S3. Increased apoptosis and decreased phospho-Akt levels in LRP1 knocked down GT1-7 cells. *A*, GT1-7 cells were transfected with LRP1 siRNA or control, non-targeting siRNA. Seventy-two hours after transfection, media was changed to normal serum containing media (+FBS) or DMEM-only media (-FBS). Twenty-four hours later, levels of LRP1, phospho-Akt, full-length caspase-3 and cleaved caspase-3 were analyzed by Western blot. *B*, cell viability was assessed by the MTT reduction assay in sister cultures treated as in *A*. Mean differences were compared by ANOVA and Dunnett's test using control siRNA + FBS cells as the reference group (** $p < 0.01$) or by ANOVA and Bonferroni´s test for selected groups (# $p < 0.05$).

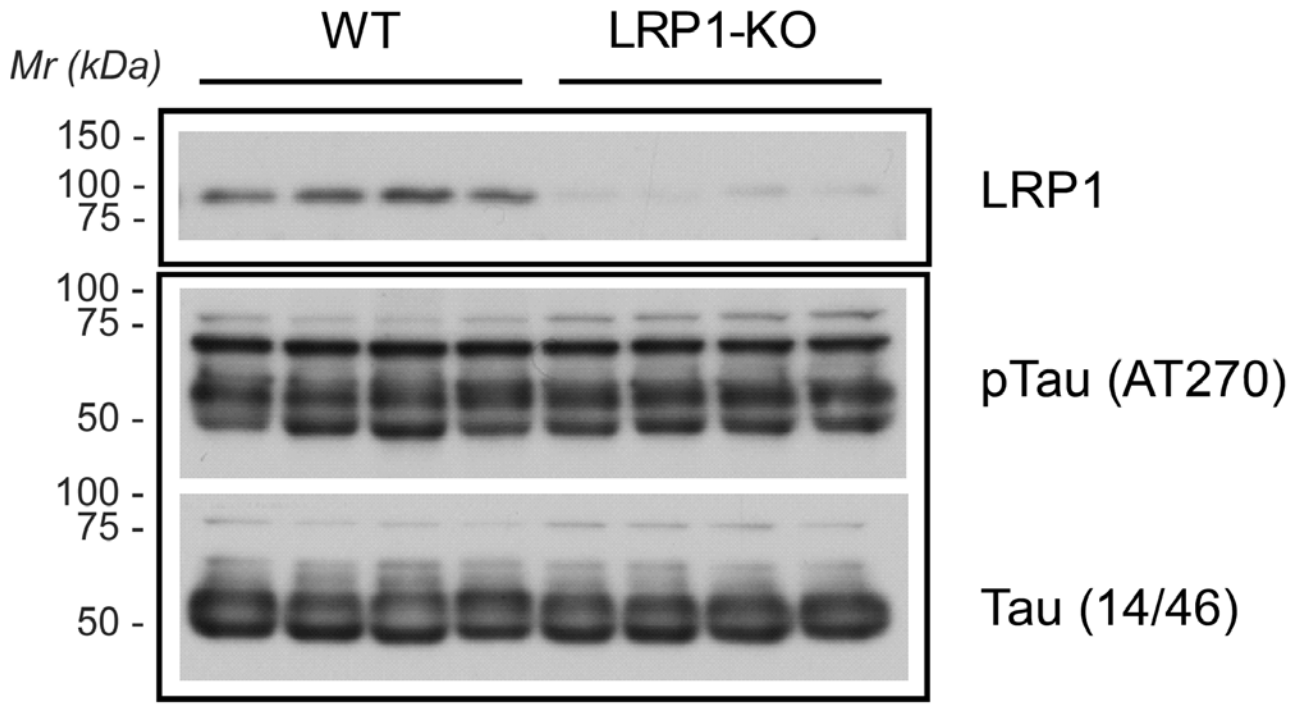

Figure S4. Tau phosphorylation in LRP1 forebrain knockout mice. Equal amounts (20 μg) of cortical homogenates from conditional LRP1 forebrain knockout mice (LRP1-KO, n=4) and control wild type littermates (WT, n=4) were subjected to SDS-PAGE and LRP1, phospho Tau (AT270 epitope) and total Tau levels were determined by Western blot analysis. No significant differences in the levels of phosphorylated tau and total tau was detected between LRP1-KO and controls.

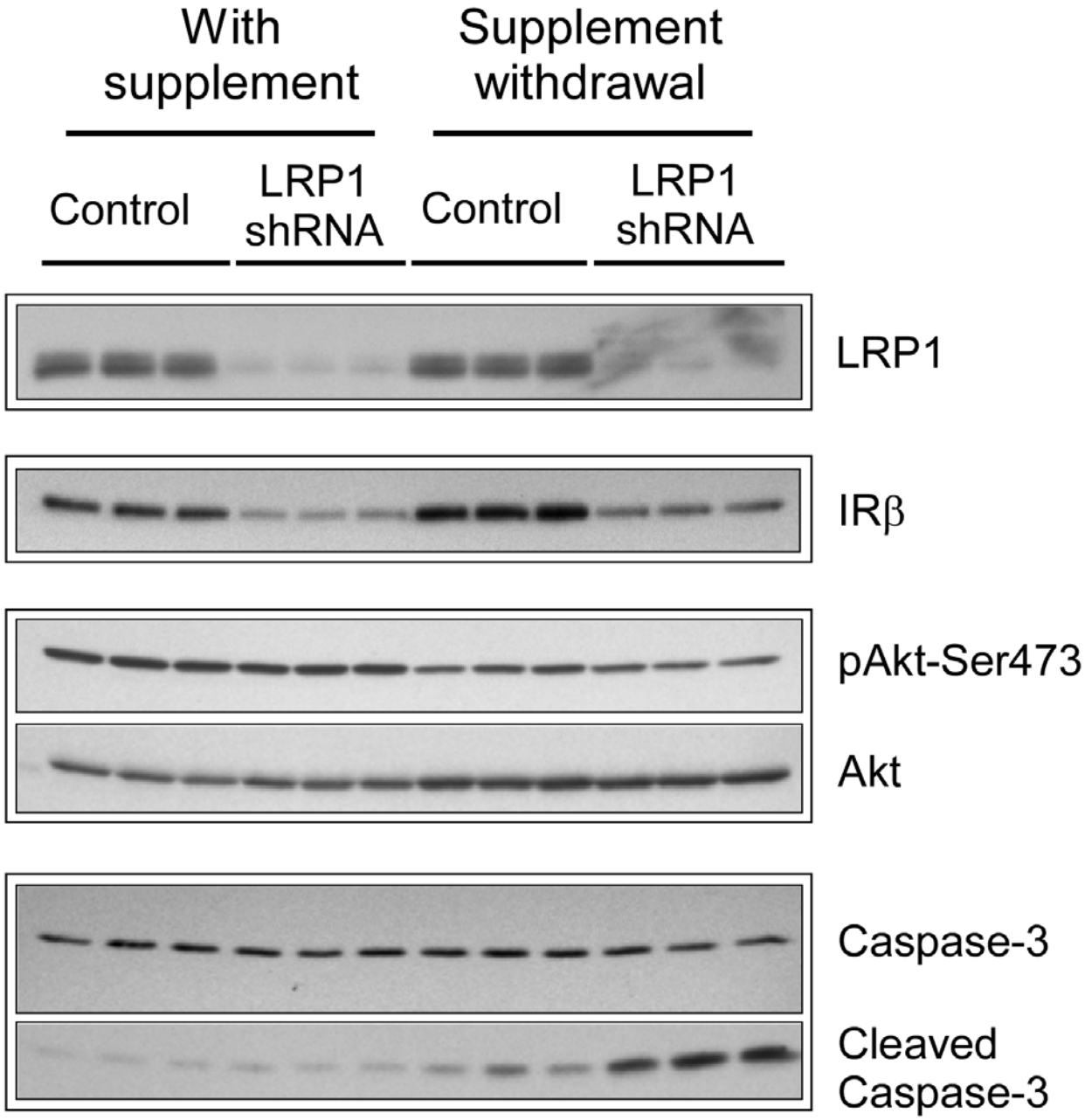

Figure S5. Increased apoptosis and decreased insulin receptor and phospho-Akt levels in LRP1 knocked down neurons with LRP1 shRNA #1. Primary neurons were infected with control or LRP1 shRNA target #1 and the levels of LRP1, insulin receptor, phospho-Akt, total Akt, full-length caspase-3 and cleaved caspase-3 were analyzed by Western blot under conditions of both control and upon 18 h treatment with Neurobasal-only media.

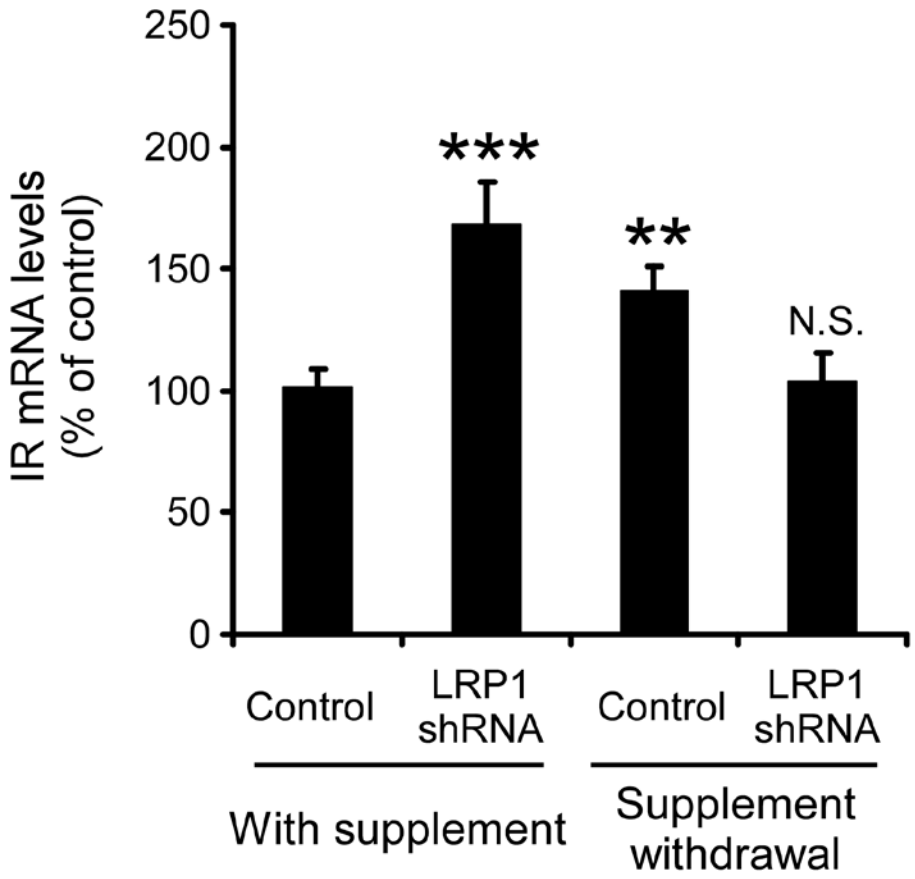

Figure S6. Insulin receptor mRNA levels in LRP1 knocked down neurons. Total RNA was extracted from experiments as in Figure 5 and mRNA levels of the insulin receptor were determined by quantitative PCR and plotted relative to control neurons. Values are mean ± SEM from triplicate determinations from three independent experiments. Mean differences were compared by ANOVA and Dunnett's test using control lentivirus + supplement as the reference group. ** $p < 0.01$, *** $p<0.001$.