Supplementary Methods

Immunoblots. COS-7 cell lysates were resuspended in phosphate buffered saline, pH 7.2, containing protease inhibitors (Roche Diagnostics, Lewes, UK) and 2mM EDTA. Aliquots were taken for assay of total protein (BCA, Pierce) and the remainder of each sample was solubilized in sample buffer for SDS-PAGE. DRG neurons, incubated with IGF-1 (200 ng/ml; Sigma) were directly lysed in the culture plates using 1X SDS sample buffer (60 mM Tris HCl, pH 6.8; 2% SDS; 2% β-2 mercaptoethanol; 0.005% Bromophenol blue). The samples were sonicated briefly (3 x 10 sec. on ice) and centrifuged (10,000 x g, 10min., 4°C). Samples (30 _g total protein) were separated by SDS-PAGE on 4-12% gradient gels and then transferred electrophoretically to PVDF membranes. After blocking the membranes (3% BSA, 3hours at 55°C) they were incubated with a 1:1000 dilution of antibody to the II-III linker of rabbit Cav2.2 α1, followed by secondary antibody (1:3000 dilution of goat anti-rabbit IgG-horseradish peroxidase conjugate, Bio-Rad). Membranes blocked with 3% BSA for 1 h at room temperature were incubated overnight at room temperature with 1:1000 dilution of either anti-β2a17 or anti-Akt/PKB (Cell Signalling Technology, Beverley, MA) or anti-p110γ (Santa Cruz Biotchnology, Inc. Santa Cruz, CA) or anti EE (Covance, Berkeley, CA), followed by secondary antibody (1:1000 dilution of Fluorolink Cy5 labelled goat anti-rabbit IgG, Amersham Pharmacia Biotech (APB), Little Chalfont, UK). Incubation with either anti-Phospho-Ser473 Akt/PKB or anti-Phospho-Thr308 Akt/PKB antibody (1:1000 dilution overnight at 4°C, Cell Signaling Technology ) was followed by 1:1000 dilution of goat anti mouse IgG-horseradish peroxidase conjugate secondary antibody. Bound antibodies were detected using ECL plus (APB). The immunoblots were imaged on a Typhoon 9410 variable mode imager (APB) in fluorescence or chemiluminescence mode and Cav2.2 α1 protein bands were quantified using Imagequant V.5.0 (APB) in volume quantitation mode.

Metabolic labeling with 33P and immunoprecipitation. Transiently transfected COS-7 cells were washed and incubated with phosphate-free DMEM (ICN Biochemicals, Irvine, CA) containing 10% dialysed FBS (Invitrogen). After 1 h, the medium was replaced with phosphate-free DMEM containing 30µCi/ml [33P] orthophosphate and incubated for 6 h. Labeled cells were washed twice with TBS containing protease inhibitors and 1mM EDTA, harvested and stored at -80°C.

For immunoprecipitation, cells were resuspended and lysed by passing them through a fine needle in 1.5 ml of buffer containing 20mM Tris-HCl pH 7.4, 150mM NaCl, 1mM EDTA, 1% Igepal, 1mM sodium orthovanadate, 50µM cantharidic acid, 20µM bromotetramisole oxalate and protease inhibitors. After centrifugation at 20,000 x g for 20 min at 4°C, lysates were subjected to immunoprecipitation using 3µg anti-HA High Affinity antibody (Roche Diagnostics). The resulting complexes were washed four times with lysis buffer and resuspended in100µl of 1X SDS sample buffer.
The amount of $^{33}$P incorporated in each condition was corrected by the amount of Ca$_v$β$_{2a}$ protein immunoprecipitated and expressed as a percentage change relative to the $^{33}$P incorporated in Ca$_v$β$_{2a}$ subunits in the absence of PI3Kγ (Fig. 5g).

**Co-immunoprecipitation.** HA-Ca$_v$β$_{2a}$ was immunoprecipitated with 2µg anti HA High Affinity antibody. The immune complexes were washed three times with lysis buffer and once with lysis buffer containing 500mM NaCl before resuspension in 100µl of 1 x SDS sample buffer. The co-precipitating Akt/PKB protein was detected by immunoblotting with anti-Akt/PKB.