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Improved calcium sensor GCaMP-X overcomes the calcium channel perturbations induced by the calmodulin in GCaMP

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GCaMP, one popular type of genetically-encoded Ca^{2+} indicator, has been associated with various side-effects. Here we unveil the intrinsic problem prevailing over different versions and applications, showing that GCaMP containing CaM (calmodulin) interferes with both gating and signaling of L-type calcium channels (Ca_V1). GCaMP acts as an impaired apoCaM and Ca^{2+}/CaM, both critical to Ca_V1, which disrupts Ca^{2+} dynamics and gene expression. We then design and implement GCaMP-X, by incorporating an extra apoCaM-binding motif, effectively protecting Ca_V1-dependent excitation–transcription coupling from perturbations. GCaMP-X resolves the problems of detrimental nuclear accumulation, acute and chronic Ca^{2+} dysregulation, and aberrant transcription signaling and cell morphogenesis, while still demonstrating excellent Ca^{2+}-sensing characteristics partly inherited from GCaMP. In summary, CaM/Ca_V1 gating and signaling mechanisms are elucidated for GCaMP side-effects, while allowing the development of GCaMP-X to appropriately monitor cytosolic, submembrane or nuclear Ca^{2+}, which is also expected to guide the future design of CaM-based molecular tools.

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