Combined calpain-induced downregulation of TrkB-FL and TrkB-T1 upregulation causes neuronal death in excitotoxicity and ischemia

We would like to thank the authors of this article for their recognition of our previous work (Vidaurre et al., 2012), by means of an addendum which acknowledges the similarity of some of their results to our findings regarding the calpain-induced downregulation of TrkB-FL and the upregulation of truncated forms of the TrkB receptor produced upon ischemia and excitotoxicity. However, there are still important issues concerning the mechanism of TrkB dysregulation and the consequences it has on neuronal survival that need to be considered.

We have directly established that TrkB-FL (145 kDa) is a novel calpain substrate and demonstrated that cleavage occurred nearby the divergence point of TrkB-FL and TrkB-T1 sequences, resulting in a truncated TrkB-FL (95 kDa) that lacked the tyrosine kinase domain and was strikingly similar to TrkB-T1. Therefore, in excitotoxic conditions, this TrkB-FL fragment contributes to the observed increase of truncated TrkB forms, all of them recognized by panTrkB antibodies directed to extracellular TrkB domains. Since this catalitically inactive TrkB-FL fragment might act as a dominant-negative protein in BDNF signaling together with TrkB-T1, it needs to be carefully considered to establish the impact on neuronal death of TrkB regulation induced by ischemia.

Additionally, the paper by Gomes et al. proposes a neuroprotective activity for truncated TrkB receptors, induced by BDNF at early times of excitotoxic activation in vitro. However, our results obtained in human stroke suggested an association of TrkB-T1 upregulation with neurodegeneration which could be demonstrated in a model of ischemia. To further analyze how the dysregulation of TrkB isoforms contributed to excitotoxic death, we reverted these changes using lentiviruses which allowed the neurospecific synthesis of recombinant TrkB-FL and/or the interference of TrkB-T1 expression. We demonstrated that only the combined strategy was able to produce a significant and reproducible protection from excitotoxic insults. These data implicate a combination of TrkB-FL downregulation and TrkB-T1 upregulation as a significant cause of neuronal death in excitotoxicity.

Reference

Vidaurre OG, Gascon S, Deogracias R, Sobrado M, Cuadrado E, Montaner J, Rodriguez-Pena A, Diaz-Guerra M. (2012) Imbalance of neurotrophin receptor isoforms TrkB-FL/TrkB-T1 induces neuronal death in excitotoxicity. Cell Death and Disease 3:e256