Involvement of prokineticin 2 in amyloid beta-induced neurotoxicity

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BV8/Prokineticin 2 (PK2) is a bioactive peptide that exerts its actions by binding to two G-protein coupled receptors called prokineticin receptor 1 (PKR1) and prokineticin receptor 2 (PKR2).
PK2, initially discovered as a regulator of gastrointestinal motility, is involved in multiple biological roles including circadian rhythms, angiogenesis and neurogenesis. Recently, PK2 has been identified as a deleterious mediator for cerebral ischemic injury. Indeed, PK2 can be activated by pathological stimuli such as inflammation, hypoxia-ischemia and excitotoxic glutamate in primary cortical cultures. Because a number of pathological insults could activate PK2, it has been suggested that it may be a mediator in other neurological/neurodegenerative diseases.
Aim of the present study was to evaluate the PK2 potential involvement in amyloid beta (Aß) neurotoxicity, the characteristic Alzheimer's disease (AD) insult.
Using primary cortical cultures, we found that PK2 mRNA is up-regulated by Aß peptide, suggesting its potential involvement in AD. We therefore characterized, by immunofluorescence, the presence of both PKR1 and PKR2 receptors in cortical neurons. In view of their presence, we tested the neuroprotective activity of a PKR receptor antagonist (PC1) against neuronal death induced by Aß. We found that PC1 dose-dependently protects cortical neurons against both $Aß_{25-35}$- and $Aß_{1-42}$-induced neurotoxicity, as revealed by live/dead cell assay and Hoechst staining. Electrophysiological experiments showed that the Aß-induced increase of kainate current amplitude was reversed by PC1 treatment. Moreover, PC1 completely rescued LTP impairment in hippocampal slices from 6 month-old Tg2576 AD mice without affecting basal synaptic transmission and paired pulse-facilitation paradigms.
These results indicate that PK2 plays a role in Aß-mediated neuronal death and that the prokineticin receptor antagonists may represent a new approach in the understanding and treatment of AD.