Involvement of the Prokineticin system in *in vitro* and *in vivo* models of Aβ-induced neurotoxicity

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There are growing evidence that chemokines and chemokine receptors are up-regulated in central nervous system during AD, which may contribute to plaque-associated inflammation and neurodegeneration [1].
Prokineticin 2 (PK2) belongs to a new family of chemokines which activate two GPCRs: PKR1 and PKR2, localized on cortical brain neurons and astrocytes, dorsal root ganglia, granulocytes, macrophages and endothelial cells. We have already demonstrated that PK2 is strongly up-regulated in neutrophils by inflammatory stimuli [2] and in neurons and glial cells in DRG and spinal cord by peripheral nerve injury [3]. It was also reported that PK2 mRNA expression was up-regulated by several pathological stressors, including hypoxia and reactive oxygen species in neurons and astrocytes primary cultures [4].
Aim of the present study was to investigate the involvement of the Prokineticin system *in vitro* and *in vivo* models of Aβ-induced neurotoxicity.
Using primary cortical cultures (CNs), Incubation of CNs with $A\beta_{1-42}$ (20mM) for 48 h caused a 55% reduction in the number of surviving cells. PC1, a PKR1 preferring antagonist, dose-dependently (50, 100, 250 and 500 nM) reversed the $A\beta_{1-42}$ toxicity. Time-course analysis (6, 12, 24h) of expression levels of PK2 and PKRs in CNs treated with $A\beta_{1-42}$ (20mM) indicated that both PK2 and PKRs mRNA were significantly increased after 6 and 24h $A\beta_{1-42}$ exposure, respectively. By immunofluorescence studies we demonstrated that 12h, 24h and 48h $A\beta_{1-42}$ treatment time-dependently increased PK2 and PKR2 in both neurons andastrocytes. Conversely, PKR1 immunoreactivity appeared increased only in neurons. Co-incubation with $A\beta_{1-42}$ and PC1 (100 nM) prevented the Aβ-induced PK2 mRNA and PK2 immunoreactivity up-regulation. in TG2576 mice, a transgenic AD mouse line reported to display cognitive deficits, and presence of insoluble Aβ in the brain, we found a significant increase of PK2 and PKR2in brain cortex of mice at 6 and 20 months of age.
We also examine whether systemic treatment with PC1 can result in recovery from memory deficit induced by i.c.v. injection of Aβ in rats. Rats were early infused with $A\beta_{1-42}$ or its vehicle and administered s.c. with PC1 (150 μg/Kg, twice/day) or its vehicle for 14 days starting from the day of the surgery. The Morris water maze task was carried out 4 weeks after $A\beta_{1-42}$ inoculation. Aβ/PC1–treated rats showed an ameliorated performance, respect to Aβ/saline-treated rats, when long-term memory was tested.
These results indicate that PK2 plays a role in Aβ-mediated neuronal death and that PKR antagonists may represent a new approach in the understanding and treatment of AD.

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3. Maftei et al. (2014) *Br J Pharmacol.*
4. Cheng et al., (2012) *PNAS*, 109: 5475-80