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Chronic administration of BU224, an imidazoline type-2 receptor ligand, reverses memory deficits without affecting amyloid deposition in the 5XFAD mouse model of Alzheimer's disease

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Introduction: Imidazoline type-2 receptors (I2Rs) in the brain are localized to the mitochondrial outer membrane in astrocytes (1) and regulate GFAP expression (2). Activation of these receptors seems to have neuroprotective properties including anti-apoptotic and anti-inflammatory effects. Recent evidence supports the use of I2Rs drugs as a potential therapy in Alzheimer's disease (AD).

Methods: 6 month old female transgenic 5XFAD mice, overexpressing the human amyloid precursor protein (APP695) with Swedish, Florida and London, as well as human Presenilin1 with M146L and L286V familial mutations, and wild-type controls (n=10 per group) were treated intraperitoneally with 5 $mg.kg^{-1}$ BU224 or vehicle twice a day for a period of 10 days (3). Following this, hippocampal-dependent memory was tested and mice were anesthetized, perfused and brains extracted for immunohistochemical (IHC) assessment and protein quantification by Western blot and ELISA. *In vitro* assays for calcium imaging in N2a cells incubated with BU224 (5 µM) were performed. The analysis of the behavioral tests and IHC was blinded. Depending on the data sets, statistical analyses were performed using unpaired Student's t-tests, one-way ANOVAs with Bonferroni's corrections or two-way ANOVAs with Tukey's or Bonferroni's corrections.

Results: BU224-treated 5XFAD mice showed improved spatial and perirhinal cortex-dependent recognition memory compared with vehicle treated mice, based on a significant increase in exploring the displaced object on testing day (35% increased exploration relative to non-displaced object, $P<0.02$; n=10-11). Fear conditioning testing also revealed that both hippocampal-dependent and -independent memory functions in the 5XFAD mice were also improved by BU224 following learning by association (40% greater immobility, $P<0.002$). In hippocampal and cortical homogenates, BU224 induced a decrease in the levels of certain cytokines such as IL-1β (30% reduction) and TNF-α (80% reduction in mRNA levels). These beneficial effects were not mediated by changes in amyloid pathology, neuronal apoptosis, mitochondrial density or autophagy levels. However, calcium imaging experiments in neuroblastoma cells showed a 3-fold reduction on Aβ-induced functional changes in NMDA receptors after BU224 treatment ($P<0.0001$).

Conclusions: Our data indicate that chronic treatment with BU224 improves memory and cognitive performance and reduces inflammation, at stages where these animals already have high amyloid-β deposition. Therefore, I2-imidazoline drugs could have potential benefits for AD patients

References:

(1) Regunathan S *et al.* (1993) *J Neurosci Res* **34**: 681-688.
(2) Olmos G *et al.* (1994) *Br J Pharmacol* **111**: 997-1002.
(3) Finn DP *et al.* (2003).*Psychopharmacology* (Berl) **167**:195-202.