Resveratrol as molecular competitor of PIB on the binding sites of the amyloid plaque

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Background

Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a polyphenolic compound found in juice and wine from dark-skinned grape crops, has been shown to have a neuroprotective role on in vitro and in vivo studies. Moreover, it has been found that resveratrol protects, concentration-dependently, against amyloid-β induced toxicity in cultured neurons, wich plays a critical role in the neuropathology of Alzheimer's disease (AD).

PET imaging of fibrillar amyloid-β depositions in human brain, has enabled the early detection of amyloidosis. ^{11}C-Pittsburgh compound B (PIB) is the most widely used amyloid-β tracer.

Based on the structural similarity between resveratrol and PIB (Figure 1), we studied if the binding of PIB to human brain amyloid could be influenced by resveratrol.

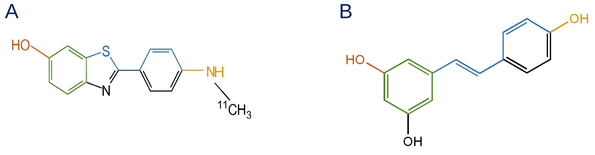

Figure 1. (A) N-Methyl- [^{11}C] 2-(4'-methylaminophenyl)-6-hydroxybenzothiazole ([^{11}C] PIB). (B) 3,5,4'-trihydroxy-trans-stilbene (Resveratrol).
Structural elements shared between displayed structures are highlighted.

Objective

To determine the *in vitro* affinity of resveratrol to the [^{11}C]PIB amyloid binding sites using quantitative autoradiography studies in postmortem human brain sections of patients with AD.

Materials & Methods

In vitro autoradiography studies were performed on frozen unfixed serial brain sections (20 µm) from postmortem middle frontal cortex of patients with familial AD (courtesy of the Brain Bank of FLENI, Argentina). The presence of β amyloid was confirmed histopathologically.

Autoradiographic displacement studies with [^{11}C]PIB as tracer and resveratrol as competitor were done. To assess the effect of resveratrol to the binding of [^{11}C]PIB, the tissues were treated with resveratrol for 5min at increasing concentrations: 0.1, 1, 10, 100, 1000, 10000 nM. Then, they were incubated with [^{11}C]PIB (0.3 MBq/mL) for 40 minutes.

Alternatively, displacement studies of [^{11}C]PIB by "cold" PIB (concentrations studied: 0.01, 0.1, 1, 10, 100, 1000, 10000 nM) were evaluated (Figure 2). For each replicated experiment (N=3), at least 3 tissue slices were sampled.

Slides were exposed to HS screen. The images were acquired on a Phosphor Imager and analyzed using a computer-based image analysis system (ImageQuant TL).

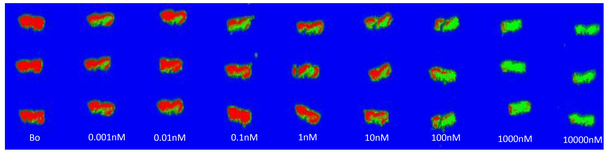

Figure 2. Displacement study of [^{11}C]PIB by "cold" PIB.

Results

We observed that resveratrol blocked the binding of [^{11}C]PIB to amyloid in AD human brain cortex. The inhibition was dose-dependent. An inhibition of 97% was observed with a concentration of 100 nM of resveratrol and a total blockade with 1000 nM.

Displacement or inhibition studies revealed an affinity (IC50) value of (31±10) nM for resveratrol, and (3,3±1,3) nM for PIB (Figure 3).

Conclusions

Resveratrol had a competitor effect concerning the [^{11}C]PIB binding sites. A total blocking was reached at the highest dose. However, PIB was found to have 10-fold more affinity than resveratrol to the amyloid binding sites.

Further studies of the effects of resveratrol in amyloid depositions *in vivo* AD are necessary.

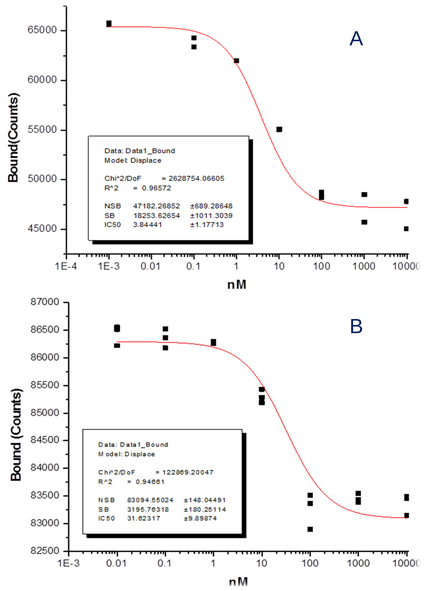

Figure 3. PIB compound was found to have 10-fold more affinity than resveratrol to binding sites of amyloid plaques in AD human brain cortex.
(A) Displacement of [^{11}C]PIB by "cold" PIB. (B) Displacement studies with [^{11}C]PIB as tracerand resveratrol as competitor.

References

1. Neuroprotective effects of resveratrol againstb-amyloid-induced neurotoxicity in rat hippocampal neurons: involvement of protein kinase C, British Journal of Pharmacology.
2. Amyloid tracers detect multiple binding sites in Alzheimer's disease brain tissue, Brain.