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Carvedilol as a potential novel agent for the treatment of Alzheimer's disease

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Abstract

Oligomeric β-amyloid (Aβ) has recently been linked to synaptic plasticity deficits, which play a major role in progressive cognitive decline in Alzheimer's disease (AD). Here we present evidence that chronic oral administration of carvedilol, a nonselective β-adrenergic receptor blocker, significantly attenuates brain oligomeric β-amyloid content and cognitive deterioration in 2 independent AD mouse models. We found that carvedilol treatment significantly improved neuronal transmission, and that this improvement was associated with the maintenance of number of the less stable "learning" thin spines in the brains of AD mice. Our novel observation that carvedilol interferes with the neuropathologic, biochemical, and electrophysiological mechanisms underlying cognitive deterioration in AD supports the potential development of carvedilol as a treatment for AD.
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1. Introduction

Alzheimer's disease (AD) is a devastating neurological disorder that imposes a tremendous health burden on society. Currently available palliative medications have not demonstrated significant beneficial effects in AD (Lyketsos et al., 2004) and treat symptoms only.

Growing evidence suggests that cognitive deterioration in AD is directly linked to the accumulation of extracellular soluble oligomeric β-amyloid (Aβ) species, rather than amyloid plaque deposition in the brain (Cleary et al., 2005; Gylys et al., 2003; Klyubin et al., 2005; Kotilinek et al., 2002; Lambert et al., 1998; Lesne et al., 2006; Shankar et al., 2008). Oligomeric Aβ induces synapse degeneration and synaptic plasticity disruption, which contribute to mechanisms underlying the onset and progression of dementia in AD (Coleman et al., 2004; Jacobsen et al., 2006; Lacor et al., 2004; Scheff and Price, 2003; Selkoe, 2002; Shankar et al., 2007, 2008; Terry et al., 1991; Walsh et al., 2002). Thus, interference with oligomeric Aβ formation

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presents a viable preventative and/or therapeutic strategy for AD dementia (Klein, 2002; McLaurin et al., 2006; Seabrook et al., 2007; Zhao et al., 2009).

Carvedilol is a nonselective β-adrenergic receptor blocker, widely prescribed for treating congestive heart failure and hypertension (Packer et al., 1996). Previous structural analysis suggested that carvedilol possesses a specific 3-dimensional pharmacophore conformation, associated with the ability to bind Aβ and prevent Aβ from forming oligomeric fibrils (Howlett et al., 1999). A recent study suggested that use of carvedilol is associated with cognitive benefits in AD patients (Rosenberg et al., 2008). In the present study, we explored the potential beneficial role of carvedilol in AD neuropathology and cognitive deterioration in mouse models of AD, in addition to the potential mechanism associated with its beneficial effect.

2. Methods

2.1. Animals

TgCRND8 transgenic mice carrying a human amyloid precursor protein (APP) containing a familial AD double mutation (Swedish KM670/671NL and Indiana V717F) (Chishti et al., 2001), expressed under the control of a prion promoter, were generated by mating TgCRND8 males with wild type (WT) females (Charles River, Wilmington, MA). The offspring of the wild-type and heterozygous TgCRND8 were genotyped at 30 days of age. A second, independent AD mouse model (Tg2576 AD transgenic mice) engineered to express APP containing the familial AD Swedish mutation (Hsiao et al., 1996) were purchased from Taconic (Taconic Farms, Germantown, NY).

All mice were housed with food and water available ad libitum, and maintained on a 12-hour light/dark cycle with lights on at 7:00 AM in a temperature-controlled (20 ± 2 °C) room prior to experimental manipulation. All procedures and protocols were approved by the Mount Sinai School of Medicine's Institutional Animal Care and Use Committee (IACUC) through the Center for Comparative Medicine and Surgery.

2.2. Carvedilol treatment

Female TgCRND8 mice were treated with 1.5 mg/kg/day of carvedilol delivered in their drinking water, starting at 8 weeks of age. Using US Department of Agriculture-recommended formulation for converting equivalent drug dosage between species, 1.5 mg/kg/day is equivalent to 7.5 mg per day in human (US Food and Drug Administration: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078932.pdf). TgCRND8 mice were assigned to 2 groups: carvedilol treatment and water control groups. Animals had free access to both liquid and standard chow. Drinking solutions were changed once every week. After 5 months of treatment, mice were sacrificed by decapitation. Brains were harvested as previously described (Wang et al., 2005). Tg2576 mice were treated with the same dose of carvedilol for 7 months, starting at 5 months of age.

2.3. Photoinduced cross-linking of unmodified proteins assay (PICUP)

Freshly isolated low molecular weight $A\beta_{1-42}$ (10–20 μM) or $A\beta_{1-40}$ (30–40 μM) peptides were mixed with 1 μL of 1 mM tris (2,2′-bipyridyl) dichlororuthenium (II) (Ru(bpy)) and 1 μL of 20 mM ammonium persulfate (APS) in the presence or absence of equal molar concentration of carvedilol or 10-fold excess of carvedilol. The mixture was irradiated for 1 second, and quenched immediately with 10 μL of Tricine sample buffer (Invitrogen, Carlsbad, CA) containing 5% β-mercaptoethanol (Bitan et al., 2001). The reaction was subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis and visualized by silver staining (SilverXpress, Invitrogen, Carlsbad, CA).

2.4. Circular dichroism (CD) spectroscopy

CD spectra of Aβ:carvedilol mixtures were acquired immediately after sample preparation or following 2, 3, 6, or 7 days of incubation. CD measurements were made by removing a 200 mL aliquot from the reaction mixture, adding the aliquot to a 1 mm path length CD cuvette (Hellma, Forest Hills, NY), and acquiring spectra in a J-810 spectropolarimeter (JASCO, Tokyo, Japan). The CD cuvettes were maintained on ice prior to introduction into the spectrometer. Following temperature equilibration, spectra were recorded at 22 °C from ~190 to 260 nm at 0.2 nm resolution with a scan rate of 100 nm/minute. Ten scans were acquired and averaged for each sample. Raw data were manipulated by smoothing and subtraction of buffer spectra according to the manufacturer's instructions.

2.5. Electron microscopy (EM)

A 10 μL aliquot of each sample was spotted onto a glow-discharged, carbon-coated formvar grid (Electron Microscopy Sciences, Hatfield, PA) and incubated for 20 minutes. The droplet then was displaced with an equal volume of 2.5% (v/v) glutaraldehyde in water and incubated for an additional 5 minutes. Finally, the peptide was stained with 8 μL of 1% (v/v) filtered (0.2 mm) uranyl acetate in water (Electron Microscopy Sciences). This solution was wicked off and then the grid was air-dried. Samples were examined using JEOL CX100 transmission electron microscopy (JEOL Skandinaviska AB, Sollentuna, Sweden).

2.6. Bioavailability of carvedilol

Mouse brain specimens were harvested and carvedilol was extracted from homogenized brain tissue with diethyl ether (3×). Ether fractions were combined and frozen at −80 °C for 20 minutes, after which extracts were filtered, dried under vacuum, and resolublized in 400 μL mobile

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