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ORIGINAL PAPER

In vitro and in silico inhibition of angiotensin-converting enzyme by carbohydrates and cyclitols

[a,b]Denise C. Endringer*, [b]Osmair V. Oliveira, [a]Fernão C. Braga

[a] *Faculty of Pharmacy, Universidade Federal de Minas Gerais, Belo Horizonte, Av. Antônio Carlos, 6627, CEP 31270-901, Brazil*

[b] *Instituto Federal do Espírito Santo – campus Vila Velha, Vila Velha, Av. Ministro Salgado Filho, s/n, CEP 29106-010, Brazil*

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Fifteen carbohydrates (D-mannose, D-glucose, D-galactose, methyl-α-D-glucose, L-rhamnose, D-xylose, D-fructose, D-arabinose, dulcitol, mannitol, β-maltose, α-lactose, melibiose, sucrose, and raffinose) and four cyclitols [L-(+)-bornesitol, *myo*-inositol, per-*O*-acetyl-1-L-(+)-bornesitol, and quinic acid] were assayed for in vitro ACE inhibition. Of these molecules, per-*O*-Acetyl-1-L-(+)-bornesitol, quinic acid, methyl-α-D-glucose, D-rhamnose, raffinose, and the disaccharides were determined to be either inactive or weak ACE inhibitors, whereas L-(+)-bornesitol, D-galactose, D-glucose, and *myo*-inositol exhibited significant ACE inhibition. Molecular docking studies were performed to investigate interactions between active compounds and human ACE (Protein Data Bank, PDB 1O83). The results of various calculations showed that all active sugars bind to the same enzyme region, which is a tunnel directed towards the active site. With the exception of *myo*-inositol (K_i = 13.95 μM, IC_{50} = 449.2 μM), the active compounds presented similar K_i and IC_{50} values. D-Galactose (K_i = 19.6 μM, IC_{50} = 35.7 μM) and L-(+)-bornesitol (K_i = 25.3 μM, IC_{50} = 41.4 μM) were the most active compounds, followed by D-glucose (K_i = 32.9 μM, IC_{50} = 85.7 μM). Our docking calculations are in agreement with the experimental data and show a new binding region for sugar-like molecules, which may be explored for the development of new ACE inhibitors.

Keywords: ACE inhibition, carbohydrates, cyclitols, docking calculations

Introduction

Angiotensin converting enzyme (ACE) is an integral membrane glycoprotein expressed on the surface of epithelial and endothelial cells, which plays a crucial role in the homeostatic mechanism of mammals by modulating their renin–angiotensin system (Hooper & Turner, 2003; Brown & Hall, 2005; Vermeirssen et al., 2002). This enzyme increases the blood pressure of mammals by catalyzing the conversion of the inactive decapeptide angiotensin I into the active octapeptide angiotensin II, a potent vasoconstrictor (Koike et al., 1980; Brown & Hall, 2005; Fleming, 2006; Akif et al., 2010). Angiotensin II activates the AT1 receptor, which leads to the secretion of aldosterone, promoting sodium and water retention in the kidneys, and increasing the pressure of arteries (Brown & Hall, 2005; Fleming, 2006; Akif et al., 2010). Inhibition of ACE is considered to be an important therapeutic approach to hypertension control.

ACE inhibitors (captopril, enalapril, lisinopril, and ramipril) are widely used for the treatment of cardiovascular diseases. However, synthetic ACE inhibitors are known to present side effects such as coughing, taste disturbances and skin rashes (Brown & Hall, 2005; Alderman, 1996). Thus, new ACE inhibitors that exhibit better pharmacological and toxicological profiles, including natural compounds found in edible species and medicinal plants, are searched for. Peptides isolated from the venom of the Brazilian viper *Bothrops jararaca* have been used as templates for the development of captopril and other ACE in-

*Corresponding author, e-mail: denise.endringer@ifes.edu.br