Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
The International Journal of Biochemistry & Cell Biology 37 (2005) 1656–1669
IJBCB
www.elsevier.com/locate/biocel

The influence of phospholipid membranes on bovine calcitonin peptide's secondary structure and induced neurotoxic effects

Steven S.-S. Wang [a,*], Theresa A. Good [b], Dawn L. Rymer [c]

[a] *Department of Chemical Engineering, National Taiwan University, No 1 Sec 4, Roosevelt Rd, Taipei 10617, Taiwan*
[b] *Department of Chemical and Biochemical Engineering, The University of Maryland, Baltimore County (UMBC), Baltimore, MD 21250, USA*
[c] *Department of Chemical Engineering, Texas A&M University, College Station, TX 77843, USA*

Received 4 November 2004; received in revised form 16 January 2005; accepted 8 February 2005

Abstract

The peptide hormone, calcitonin, which is associated with medullary carcinoma of the thyroid, has a marked tendency to form amyloid fibrils and may be a useful model in probing the role of peptide–membrane interactions in β-sheet and amyloid formation and amyloid neurotoxicity. Using bovine calcitonin, we found that, like other amyloids, the peptide was toxic only when in a β-sheet-rich, amyloid form, but was non-toxic, when it lacked an amyloid structure. We found that the peptide bound with significant affinity to membranes that contained either cholesterol and gangliosides. In addition, incubation of calcitonin with cholesterol-rich and ganglioside-containing membranes resulted in significant changes in peptide structure yielding a peptide enriched in β-sheet and amyloid content. Because the cholesterol- and ganglioside-rich phospholipid systems enhanced the calcitonin β-sheet and amyloid contents, and peptide amyloid content was associated with neurotoxicity, we then investigated whether depleting cellular cholesterol and gangliosides affected calcitonin neurotoxicity. We found that cholesterol and ganglioside removal significantly reduced the calcitonin-induced PC12 cell neurotoxicity. Similar results have been observed with other amyloid-forming peptides such as β-amyloid (Aβ) of Alzheimer's disease and suggest that modulation of membrane composition and peptide–membrane interactions may prove useful in the control of amyloid formation and amyloid neurotoxicity.
© 2005 Elsevier Ltd. All rights reserved.

Keywords: Calcitonin; Amyloid; Cholesterol; Gangliosides; Secondary structure; Neurotoxicity

1. Introduction

The amyloidoses are complex, multiform disorders characterized by the polymerization and aggregation of normally innocuous and soluble proteins or peptides into extracellular insoluble fibrils. More than 16 biochemically unique proteins have been isolated as the fibrillar components of disease-associated amyloid deposits (Kelly, 1996; Lansbury, 1999; Sipe, 1994; Wetzel, 1996). While these amyloidogenic proteins exhibit little sequence or structural homology, they all produce similar, straight, unbranched amyloid fibrils

* Corresponding author. Tel.: +886 2 33665870; fax: +886 2 23623040.
E-mail address: sswang@ntu.edu.tw (S.S.-S. Wang).

1357-2725/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biocel.2005.02.006

with characteristic cross β-sheet structure and the ability to bind Congo red (Glenner, 1980a,b; Kelly, 1996; Lansbury, 1999).

A variety of evidence suggests a strong connection between amyloid fibril formation and disease pathology. The amyloid fibrils or protofibrils derived from aggregated β-amyloid (Aβ) peptides, β_2-macroglobulin, atrial natriuretic peptide, and amylin have been demonstrated to be neurotoxic in vitro (Busciglio et al., 1993; Koh et al., 1990; Liu & Schubert, 1997; Pike et al., 1991; Schubert et al., 1995; Seilheimer et al., 1997; Ueda et al., 1994; Walsh et al., 1997; Ward et al., 2000; Yankner et al., 1990). The neurotoxic effects of these peptides have been inhibited by compounds that bind to amyloid fibrils or inhibit fibril formation (Burgevin et al., 1994; Lorenzo & Yankner, 1994; Pollack et al., 1995; Sadler et al., 1995).

Calcitonin is a 32 amino acids peptide hormone whose normal functions include regulating calcium–phosphorus metabolism, potentially serving as a neuromodulator and/or a neurotransmitter in the central nervous system (Austin & Heath, 1981; Fischer et al., 1981; Rizzo & Goltzman, 1981), affecting cAMP metabolism in breast cancer cells (Lacroix et al., 1998), eliciting sperm motility and fertilizing ability (Fraser et al., 2001), and involving in the embryonic implantation process (Zhu et al., 1998). The peptide structure associated with its normal hormone functions appears to be an amphipathic helix (Epand, Epand et al., 1983, 1986a; Epand, Seyler et al., 1986; Motta et al., 1998; Siligardi et al., 1994). In addition, calcitonin receptors, containing seven-transmembrane domains, have been shown to regulate osteoclast mediated bone resorption and enhance calcium secretion by the kidney and have a strong connection with cellular signal transduction pathways (Chabre et al., 1992; Naro et al., 1998; Orcel et al., 2000; Pondel, 2000).

In vivo, calcitonin forms amyloid fibrils associated with medullary carcinoma of the thyroid (Sletten et al., 1976), which comprises approximately 7–10% of thyroid carcinomas (Fletcher, 1970; Hazard, 1977; Hill et al., 1973; Ljungberg, 1966; Ponder, 1984; Williams et al., 1966). Both intracellular and extracellular amyloid fibril deposits are associated with these tumors (Berger et al., 1988; Butler & Khan, 1986; Byard et al., 1990; Dammrich et al., 1984; DeLellis et al., 1979; Silver et al., 1988). In vitro, human calcitonin forms amyloid fibrils in physiological buffers, limiting the efficacy of human calcitonin in the treatment of osteoporosis (Arvinte et al., 1993; Bauer et al., 1994; Kanaori & Nosaka, 1995). In addition, the fibrils of human calcitonin have been shown to be toxic in cell culture (Liu & Schubert, 1997; Schubert et al., 1995).

The mechanism by which amyloids form in vivo has yet to be determined. A number of studies have shown that pH, solvent, chaperones, and/or peptide concentration all affect peptide structure and amyloid formation in vitro (Castano et al., 1995; Hamazaki, 1995; Hilbich et al., 1991; Mantyh et al., 1993; Soto et al., 1994, 1995; Wisniewski et al., 1994). In addition, a growing number of observations with the best-characterized amyloid, Aβ of Alzheimer's disease, suggest the potential importance of peptide–membrane interactions in aggregation and amyloid formation. Aβ has been observed to undergo a random-coil to β-sheet transition and accelerated amyloid formation upon binding to membranes of varying composition with both electrostatic and hydrophobic interactions being implicated (Choo-Smith & Surewicz, 1997; Choo-Smith et al., 1997; Matsuzaki & Horikiri, 1999; McLaurin & Chakrabartty, 1996; Terzi et al., 1994a,b, 1995, 1997). The presence of cholesterol and gangliosides, either in cell membrane or in culture medium, has similarly been implicated in neurotoxicity (Liu, 1999; McLaurin & Chakrabartty, 1996; Wang et al., 2001; Zhou & Richardson, 1996).

In this study, we used bovine calcitonin as a model peptide with which to investigate the role of phospholipid membranes in both the structural transition and toxicity of amyloid-forming peptides. We measured peptide-binding affinity to phospholipid membranes of varying composition and found that calcitonin had the highest binding affinity for membranes containing cholesterol and gangliosides. Hydrophobic and/or entropic effects, not electrostatic forces, probably governed the peptide–membrane interactions. We found that peptide structure was significantly influenced by peptide–membrane interactions and that those membranes to which calcitonin bound with highest affinity, cholesterol-rich and ganglioside-containing membranes, induced calcitonin to adopt structures with the greatest β-sheet and amyloid content. Based upon these observations, we then explored the links between the calcitonin–cholesterol and calcitonin–ganglioside interactions and calcitonin toxicity and found that removal of these two membrane components from PC12 cells almost completely

Download English Version:

https://daneshyari.com/en/article/9889978

Download Persian Version:

https://daneshyari.com/article/9889978

Daneshyari.com