Chapter 24  Egg-Protein-Derived Peptides with Antihypertensive Activity

ROSINA LÓPEZ-FANDIÑO, ISIDRA RECIO AND MERCEDES RAMOS

1  Introduction

Enzymatic hydrolysis of food proteins can release peptides able to exert different biological activities. Among the bioactive peptides known so far, those with blood-pressure-lowering effects are receiving special attention due to the prevalence and importance of hypertension in the Western population. Eggs are broadly recognised as a very valuable source of proteins for human nutrition and are now known to contain many substances with biological functions beyond basic nutrition. A review on biological activities of proteins and peptides derived from egg components was recently published (Kovacs-Nolan et al. 2005). This chapter discusses the production and effects of antihypertensive peptides described so far as arising from egg proteins.

2  Food Peptides with ACE-Inhibitory and Antihypertensive Effects

Hypertension is a risk factor for cardiovascular disease and stroke. As a result of an extensive research carried out during the past twenty years, a wide range of peptide sequences derived from food proteins, potentially useful in the prevention and/or treatment of hypertension, are known (Li et al. 2004). Most of these peptides act, at least in vitro, as inhibitors of angiotensin-converting enzyme (ACE, peptidyl-dipeptide hydrolase, EC 3.4.15.1), an exopeptidase that cleaves dipeptides from the C-terminal side of various oligopeptides. As part of the renin–angiotensin system, ACE hydrolyzes an inactive decapeptide, angiotensin I, to the potent vasoconstrictor angiotensin II. ACE is also part of the kinin–kallikrein system, as it hydrolyzes bradykinin, which has a vasodilator action (FitzGerald et al. 2004).

Some general features on the structure–activity relationship of ACE inhibitory peptides have been described (Meisel 1997a, b; FitzGerald et al. 2004).
ACE appears to prefer substrates or competitive inhibitors containing hydrophobic (aromatic or branched side chains) amino acid residues at each of the three C-terminal positions, and it is known that the presence of Pro as a C-terminal or antepenultimate residue enhances binding. On the other hand, ACE only binds weakly to competitive peptide inhibitors that have penultimate Pro residues. In addition, the presence of the positive charge of Lys (ε-amino group) or Arg (guanidino group) as the C-terminal residue may contribute to the inhibitory potency.

The most common strategy for the identification of novel antihypertensive food peptides is based on the preparation of protein hydrolysates and the search for fragments with in vitro ACE inhibitory activity. The in vivo effects are tested in spontaneously hypertensive rats (SHR), which constitute an accepted model for human essential hypertension. In general terms, the results of those tests have highlighted an important lack of correlation between the in vitro ACE inhibitory activity and the in vivo action. This poses doubts on the use of the in vitro ACE inhibitory activity as the exclusive selection criterion for potential antihypertensive substances, as it does not take into consideration the physiological transformations that determine the bioavailability of the peptides or the possibility of mechanisms of action other than ACE inhibition (López-Fandiño et al. 2006).

The physiological effects of ACE-inhibitory peptides depend on their ability to reach their target sites intact, which may involve survival of gastrointestinal digestion and absorption through the intestinal epithelium to get to the peripheral organs (Vermeirssen et al. 2004). The release of ACE-inhibitory peptides upon digestion of food proteins, as well as the resistance to digestion of known ACE-inhibitory sequences, have been tested in several in vitro studies showing that proteolysis by gastrointestinal enzymes is an essential factor in determining ACE-inhibitory activity (Vermeirssen et al. 2003; Gómez-Ruiz et al. 2004). In addition, the physiological effect is influenced by the action of brush-border peptidases, the recognition by intestinal peptide transporters, and the subsequent susceptibility to plasma peptidases (Pihlanto-Leppälä 2001). More research is needed in this respect, with the effort being concentrated in elucidating the pharmacokinetics and the distribution profile of ACE-inhibitory peptides in the different tissues.

Even if the hypotensive effects of food-derived ACE-inhibitory peptides have been demonstrated in SHR, only a few studies have been conducted to confirm the existence of an ACE-inhibitory mechanism in vivo (Fuglsang, et al. 2003). Furthermore, most food-derived peptides have lower ACE-inhibitory activity in vitro than the synthetic ACE inhibitor captopril, but they usually display higher in vivo activities than the efficacy levels extrapolated from the in vitro activities. This fact has been attributed to a higher affinity to the tissues and a slower elimination (Fujita and Yoshikawa 1999), but it may also be an indication of the existence of an additional mode of action, such as a direct (Kuono et al. 2005) or indirect action on vascular smooth muscle (Maes et al. 2004). It should also be mentioned that peptides