

Antihypertensive effects of whey protein



Introduction

Hypertension, or high blood pressure, affects approximately 50 million people in the US and around one billion people worldwide. Although symptoms are rarely noticeable, the effects can be serious. Sufferers are at increased risk of stroke, coronary heart disease, heart attack and kidney failure. The American Heart Association states that two thirds of Americans over the age of 65 and 10-15% of school age children are diagnosed with hypertension.

Hypertension in Europe is lower than in the US, but remains a significant problem. The prevalence of hypertension among 35 to 64 year olds is highest in Germany (55%), followed by Finland (49%), Spain (47%), England (42%), Sweden (38%) and Italy (38%). According to a report carried out in the UK, France, Germany, Italy and Sweden, the failure to achieve targets on blood pressure is resulting in 281,000 unnecessary major cardiovascular events every year [1].

Bioactivity – a positive step

The term bioactivity refers to food components that can affect biological processes or substances. They therefore have an impact on body function or condition and, ultimately, general health. Extensive research is underway to investigate the potential of bioactive components in food for improving health.

One area of interest is whey protein. Whey protein is a high quality protein source generated from milk. It is a complex blend of individual proteins, such as beta-lactoglobulin, alpha-lactalbumin, immunoglobulins, lactoferrin, lactoperoxidase and glycomacropeptide.

Whey protein is one of the highest quality proteins available for commercial use. It contains higher concentrations of branched chain amino acids (BCAAs) and essential amino acids than any other source of protein [2]. Whey protein also contains a number of peptides and whey protein fractions that may promote general health and well-being [3-5].

It is now common practice to hydrolyse protein for specific applications, such as hypoallergenic products, infant formula and clinical nutrition [6]. The hydrolysis process, which involves the breaking down of protein, can occur during gastrointestinal digestion, by fermenting milk, or through controlled reactions in the laboratory or whey processing facility.

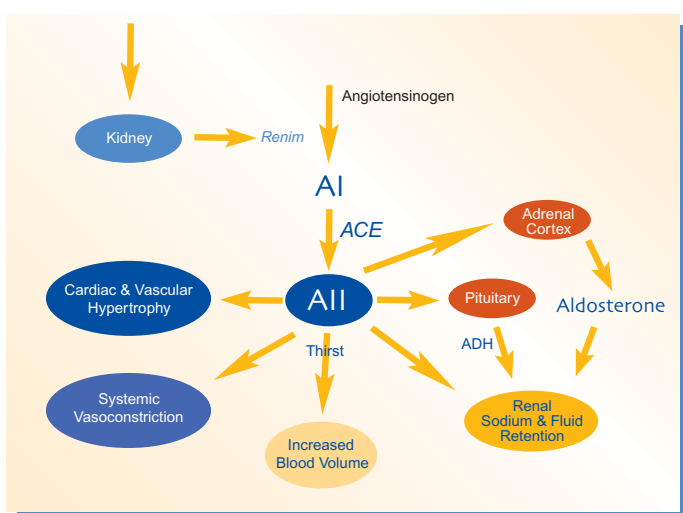
Proteins may also be hydrolysed to produce biologically active peptides, which can be added to foods as part of a complete hydrolysate or as partly purified peptides. The biological activities associated with whey peptides include cholesterol-reducing activity, antibacterial activity [7], antithrombotic activity, opioid-like activity [8], antioxidant activity and antihypertensive activity [9].

ACE inhibition

Whey protein hydrolysates contain several biologically active peptides, including antihypertensive peptides [9]. The antihypertensive effect of certain peptides has been related to the inhibition of the angiotensin converting enzyme (ACE) – a peptidyl dipeptide hydrolase. ACE activity results in an increase in blood pressure due to conversion of angiotensin 1 to angiotensin 11 – a vasoconstrictive peptide – and due to degradation of bradykinin – a vasodilative peptide.

These two actions make ACE an ideal target in the treatment of conditions such as high blood pressure, heart failure, diabetic nephropathy and type 2 diabetes mellitus. Inhibiting ACE activity results in a decrease in the level of angiotensin 11 and reduced degradation of bradykinin, leading to less restriction of blood vessels and lower blood pressure (see fig. 1).

Figure 1



Angiotensin 1 converting enzyme (ACE, EC 3.4.15.1) is an exopeptidase that catalyses the conversion of angiotensin 1 to angiotensin 11 – a potent vasoconstrictor. ACE is also involved in the inactivation of bradykinin – a potent vasodilator. Inhibition of ACE (by ACE inhibitors) results in decreased formation of angiotensin 11 and decreased inactivation of bradykinin.



Peptide diversity

It is well established that the inhibition of ACE by peptides results in a decrease in blood pressure [10]. Numerous potential ACE inhibitory peptides deduced from in vitro activity measurements have been reported [11]. Various studies describe the purification and identification of ACE inhibitory peptides from hydrolysates using different chromatographic techniques [12]. These studies suggest ACE inhibitory peptides are present in many fractions obtained using different separation principles, indicating that the molecular properties of ACE inhibitors are diverse. The fact that ACE inhibition is found in hydrolysates produced with different proteins, proteases and hydrolysis conditions indicates that a variety of peptides, with various amino acid sequences, are able to inhibit ACE [13].

Molecular weight profile of antihypertensive peptides

Most of the reported peptides exhibiting ACE inhibitory activity are of a low molecular weight (approx. < 12 amino acids). This means that active peptides can be selected to a degree by ultrafiltration, resulting in the production of a permeate stream with higher ACE inhibition than the parental hydrolysate [14]. However, with ultrafiltration, an extra processing step is introduced and the remaining retentate protein requires further treatment.

To recap, many peptides exhibit ACE inhibitory activity. The combination of these peptides determines the ACE inhibitory activity of the hydrolysates. During hydrolysis, ACE inhibitory peptides are continuously formed and degraded. Maximum ACE inhibition by the hydrolysate is a result of an optimum balance between these two processes.

Hypertension and whey protein

Several researchers have prepared enzymatic hydrolysates of whey proteins with ACE inhibitory properties by using digestive enzymes [14], microbial enzymes [15], or a combination of both [16]. Recent studies have identified whey-derived peptides as responsible for such activity [17].

A study comparing the IC₅₀ values (the amount of hydrolysate or other compound, which causes 50% inhibition of ACE activity – spectrophotometric assay) showed that a hydrolysed whey protein isolate was over 300 times more effective at inhibiting ACE than intact whey protein. This demonstrates that controlled hydrolysis of whey protein can significantly increase ACE-inhibitory activity.



Clinical Studies

The potent antihypertensive effects of both casein and whey protein hydrolysates have been demonstrated in rat studies. While there isn't extensive clinical data for human subjects, human trials have, nonetheless, shown that the administration of WPH significantly reduced systolic blood pressure. These rat and human studies are positive for whey protein and the role it has to play in managing hypertension.

Conclusions

Hydrolysate vs specific peptide

It is well established that the ACE inhibition by protein hydrolysates is the result of the inhibitory action of various peptides. Isolation of one or a few peptides with ACE inhibitory activity is therefore not justified. The method of choice for improving ACE inhibition of hydrolysates is the optimisation of the entire peptide composition of hydrolysates, since this is a method which preserves the nutritional value of the protein. Response surface modelling is proven to optimise several parameters of the hydrolysis process simultaneously, resulting in a hydrolysate with maximum ACE inhibition [13].

Whey protein vs pharmaceuticals

Food-derived peptides are considered to be milder and safer, with fewer side effects, than the drugs currently used in the treatment of hypertension. This, and the in vivo effect of peptides, need to be clarified before whey-derived peptides can be exploited in human nutrition for the prevention and treatment of hypertension [17].

References

1. Davis L. Peptide Powder. Health and Nutrition October 2003; 16 – 18
2. Bucci L and Unlu L. Proteins and amino acid supplements in exercise and sport, in energy yielding macronutrients and energy metabolism in sports nutrition. CRC Boca Raton 2002; 191 – 212
3. Florisa R et al. Antibacterial and antiviral effects of milk proteins and derivatives thereof. *Curr Pharm Des* 2003; 9 (16): 1257 – 75
4. Walzem RL, Dillard CJ and German JB. Whey components: millennia of evolution create functionalities for mammalian nutrition: what we know and what we may be overlooking. *Crit Rev Food Sci Nutr* 2002; 42 (4): 353 – 75
5. Korhonen H and Pihlanto A. Food-derived bioactive peptides: opportunities for designing future foods. *Curr Pharm Des* 2003; 9 (16): 297 – 308
6. Clemente A. Enzymatic protein hydrolysates in human nutrition. *Trends in: Food Science and Technology* 2000; 11: 254 – 262
7. Recio I and Visser S. Two ion-exchange chromatographic methods for the isolation of antibacterial peptides from lactoferrin. In situ enzymatic hydrolysis on an ion exchange membrane. *Journal of Chromatography* 1999; A (831): 191 – 201
8. Chiba H and Yoshikawa M. In RE Feeney and JR Whitaker (eds). Protein tailoring for food and medical uses. Marcel Dekker 1986; 123 – 153
9. Mullally MM, Meisel H and Fitzgerald RJ. Synthetic peptides corresponding to alpha lactalbumin and beta-lactoglobulin sequences with angiotensin 1 converting enzyme inhibitory activity. *Biological Chemistry Hoppe – Seyler* 1996; 377: 259 – 260
10. Clare DA, Swaisgood HE. Bioactive milk peptides: a prospectus. *Journal of Dairy Science* 2000; 83: 1187 – 1195
11. Kim SK, Byun HG, Park PJ and Shahidi F. Angiotensin 1 converting enzyme inhibitory peptides purified from bovine skin gelatine hydrolysate. *Journal of Agricultural and Food Chemistry* 2001; 49: 2992 – 2997
12. Matsui T, Li CH and Osajima Y. Preparation and characterisation of novel bioactive peptides responsible for angiotensin 1 converting enzyme inhibition from wheat germ. *Journal of Peptide Science* 1999; 5: 289 – 297
13. Van der Ven C, Gruppen H, Dries BA de Bont, Alphons GJ Voragen. Optimisation of angiotensin converting enzyme inhibition by whey protein hydrolysates using response surface methodology. *International Dairy Journal* 2002; 12: 813 – 820
14. Mullally MM, Meisel H and Fitzgerald RJ. Angiotensin 1 converting enzyme inhibitory activities of gastric and pancreatic proteinase digests of whey proteins. *International Dairy Journal* 1997; 7: 299 – 303
15. Abubakar A, Saito T, Aimar MV and Itoh T. New derivation of the inhibitory activity against angiotensin converting enzyme (ACE) from sweet cheese whey. *Tohoku Journal of Agricultural Research* 1996; 47: 1 – 8
16. Pihlanto – Leppala A, Rokka T and Korhonen H. Angiotensin converting enzyme inhibitory peptides derived from bovine milk proteins. *International Dairy Journal* 1998; 8: 325 – 331
17. Pihlanto A, Koskinen P, Piilola K, Tupasela T and Korhonen H. Angiotensin 1 converting enzyme inhibitory properties of whey protein digests: Concentration and characterization of active peptides. *Journal of Dairy Research* 2000; 67: 53 – 64



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