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Specifically designed peptide structures effectively suppressed oxidative reactions in chemical and cellular systems

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ABSTRACT

Peptides were designed based on the identified structural motif of the most potent antioxidant peptides derived from barley protein. Six peptides contained the effective pentapeptide QPYPQ with appended Gln and Pro residues and the other peptides possessed higher hydrophobicity. The peptides have the repetitive sequences of Q, P and Y to investigate the contribution of vicinal residues to their antioxidant capacity. Antioxidant activity of the synthetic peptides was evaluated in chemical and cellular models. Free radical scavenging assays demonstrated the positive role of QP and PY pairs in stabilizing the peptide radicals. Cellular models revealed that repetitive peptide sequences effectively inactivate lipid hydroperoxides and intracellular reactive oxygen species. Peptides with alternating residues were also found effective in inhibition of amyloid fibril formation. These results verified that in addition to the chemical structure of individual side chains, the combined effects of the vicinal residues are also important in antioxidant activity of the whole peptide.

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1. Introduction

The proper function of living cells requires the adequate monitoring and control of the intracellular redox balance. Reactive oxygen species (ROS) is a general term which describes O_2-derived free radical and non-radical species generated during respiratory chain and oxidation chain reactions occurring in cells or any lipid containing systems (Circu & Aw, 2010). There are four major radical species, including superoxide anion ($O_2^{\bullet-}$); peroxyl radical (ROO$^\bullet$); hydroxyl radical ($^\bullet$OH) and peroxynitrite ($ONOO^-$); and two non-radical species, Singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2) (Szeto, 2008). These reactive species can cause modification of various biomolecules such as nucleic acids, proteins and lipids *in vitro* or in other complex systems such as food or cosmetic products. Overproduction of ROS is considered as oxidative stress which may lead to critical damage to living organisms (Dixon & Stockwell, 2014). For example, cellular ROS are formed during mitochondrial oxidative phosphorylation which primarily generates superoxide anion ($O_2^{\bullet-}$) (Circu & Aw, 2010; Szeto, 2008). In the presence of mitochondrial superoxide dismutase (SOD), $O_2^{\bullet-}$ can be converted into H_2O_2 which can diffuse out to the cytoplasm. The highly reactive hydroxyl radical can also be generated from H_2O_2 via the Fenton reaction in the presence of metal ions (Szeto, 2008). In bacterial mutants lacking SOD, superoxide accumulation

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inhibits growth due to impaired amino acid synthesis and DNA damage (Dixon & Stockwell, 2014). Oxidative stress occurs when the oxidative damage overwhelms the antioxidant defence mechanisms (Circu & Aw, 2010). Therefore, in an oxidative stress condition, the exogenous antioxidant support is required to either protect cellular macromolecules from oxidative attack or restore indigenous antioxidant defence molecules (Je, Cho, Gong, & Udenigwe, 2015). Since oxidative stress is strongly correlated with the neurodegenerative diseases, diabetes and inflammatory disorders (Szeto, 2008), extensive research has explored the capacity of exogenous antioxidant compounds to boost the defence mechanisms of living cells. Antioxidant peptides, aside from their nutritional benefits, can suppress the oxidation reactions through various mechanisms including inactivation of reactive oxygen species, free radicals scavenging, chelation of pro-oxidative transition metals and promoting the enzymatic elimination of specific oxidants (Bamdad, Wu, & Chen, 2011).

In a related area of research, free radical reactions are shown to be the critical step in amyloid fibril formation (Ahyayauch et al., 2012). Normal cell functions are disturbed by the aberrant aggregation of proteins leading to highly ordered protein assemblies such as amyloid fibrils (Gazit, 2005). Accumulation of these supramolecular species is linked to severe pathological complications such as Alzheimer's and Parkinson's diseases (Artemova, Bumagina, Kasakov, Shubin, & Gurvits, 2010). A positive contribution of short peptide sequences in suppression of the amyloid formation has also been revealed through *in vitro* and *in vivo* experiments. One common feature of those peptides is the presence of aromatic residues that effectively interfere with the hydrophobic interactions forming the assembly (Gazit, 2005). However, the impact of antioxidant peptides on amyloid fibril formation is almost unknown.

In our previous research, protein hydrolysates derived from barley storage protein possessed a strong antioxidant capacity in different model systems. A high frequency of hydrophobic residues such as leucine (Leu, L), valine (Val, V), isoleucine (Ile, I) and proline (Pro, P) positively contributed to the free radical scavenging capacity particularly against 1,1-diphenyl-2-picrylhydrazyl (DPPH) and superoxide anion free radicals (Bamdad & Chen, 2013; Udenigwe & Aluko, 2011). Ionized side chains of glutamic acid (Glu, E) generated due to partial deamidation of glutamine (Gln, Q) residues can potentially act as a reducing agent by donating a hydrogen atom. Furthermore, these negatively charged functional groups are able to form chelates with transitional metal ions and suppress their pro-oxidative activity (Bamdad & Chen, 2013; Udenigwe & Aluko, 2011). Physicochemical characterization and sequence identification of the antioxidant peptide fractions suggest that a pentapeptide sequence (QPYPQ) common in the peptide fractions could be the structural motif of the most potent antioxidant peptides (Bamdad & Chen, 2013). Meanwhile some peptides with significantly higher hydrophobicity values were identified in potent antioxidant fractions of barley protein hydrolysate, including SVNVPLY and YRIVPL. Our previous work also revealed that similar to the chemical structure of the amino acid side chains, vicinal residues play an important role contributing to antioxidant effects (Bamdad & Chen, 2013).

In recent years great progress has been made to understand the antioxidant activity of individual amino acids and many effective sequences have been identified. However, the cumulative impact of different residues of the whole peptide and the contributions of vicinal residues on antioxidant activity are still unclear. Therefore, the main objective of the current study was to evaluate the antioxidant efficiency of the peptides containing alternating residues and investigate the effect of vicinal residues. Functional chemical models have been developed to study antioxidant effects of peptides and protein hydrolysates. Although these models of oxidation are simple and easily controllable, they cannot simulate the complicated nature of a biological system. In this study, we employed cell culture models since they more closely approximate an *in vivo* condition and are relatively easy to scale up in a controlled manner. There are few studies that have reported the antioxidant effect of the peptide fractions or a purified peptide in cell culture models (Hong, Chen, Hu, Yang, & Wang, 2014; Wiriyaphan, Xiao, Decker, & Yongsawatdigul, 2015). To the best of our knowledge, a systematic study utilizing strategically designed synthetic peptide sequences to investigate structure–function relationships in prevention of oxidation in cells has not been conducted. A clearer understanding of the structural requirements of antioxidant effects could improve the design and development of antioxidant peptides by proper selection of the starting protein and the best proteolytic enzymes. A systematic understanding of antioxidant mechanisms and how peptide sequence and structure affect their overall antioxidant effects is important for successful applications in nutraceutical and therapeutic areas.

2. Materials and methods

In this study, six peptides were designed based on our previous research (Bamdad & Chen, 2013) which revealed an effective antioxidant activity of the sequences QPYPQ. This pentapeptide, which has two distinct parts, the terminal Gln and the core part of PYP, is located in the N-terminal domain of the barley hordein, which contains short sequences of repeated Gln, Pro and Tyr (Shewry, Napier, & Tatham, 1995). As listed in Table 1, all six synthesized peptides contain the core sequence with various lengths of terminal Glns. The effect of repeated Gln residues was investigated, since the positive role of glutamine residues in antioxidant activity of peptides derived from glutamine-rich proteins, such as gluten, zein and hordein,

Table 1 – Peptide sequences synthesized manually for antioxidant evaluation.

Peptide sequences	
Alternative peptide sequences	Pro-Tyr-Pro (PYP) Gln-Pro-Tyr-Pro-Gln (QPYPQ) Gln-Gln-Pro-Tyr-Pro-Gln (QQPYPQ) Gln-Pro-Gln-Pro-Tyr-Pro-Gln (QPQPYPQ) Thr-Gln-Gln-Pro-Tyr-Pro-Gln (TQQPYPQ) Glu-Pro-Tyr-Pro-Glu (EPYPE)
Hydrophobic peptides	Ser-Val-Asn-Val-Pro-Leu-Tyr (SVNVPLY) Tyr-Arg-Ile-Val-Pro-Leu (YRIVPL)

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