Absorption of intact Bioactive Collagen Peptides® by the gut

Introduction

This paper supports the findings that Bioactive Collagen Peptides® are small specific polypeptides that can partially survive digestion and can pass the gut barrier in intact form, to ultimately exert their bioactivities at target tissues.

It is well-known that amino acids and di- and tri-peptides are well absorbed by the gut. However, the fact that also polypeptides or even larger proteins can be absorbed in a high molecular weight form is rather unknown.

Bioactive Collagen Peptides® are set apart from the broader class of food-derived polypeptides due to a special amino acid composition, which results in a unique peptide chain structure that seems to facilitate its transport across the gut wall.

Such features that make Bioactive Collagen Peptides® highly permeable are further detailed in this paper.

Key points

• Bioactive Collagen Peptides® are polypeptides of unique shape and amino acid composition that are absorbed in intact form, to some extent.
• The rare single helical structure of Bioactive Collagen Peptides®, formed by frequent Proline–Hydroxyproline–Glycine repeats, provides the favorable folding and stability that seem to facilitate its gut permeability.
• Bioactive Collagen Peptides® are remarkably rich in the amino acid Proline (¼) and it is known that Proline forms strong peptide bonds that are more resistant to be broken down by digestive enzymes.
• The true digestibility of Bioactive Collagen Peptides® is very high (98.4%). Amino acids are important products of peptide digestion, as they are the protein building blocks of new connective tissue. Approximately 10% of the Bioactive Collagen Peptides® stay intact during digestion (good bioavailability) and have a direct stimulatory impact on cell metabolism.

Bioactive Collagen Peptides® of unique composition and structure

GELITA uses an enzymatic hydrolysis process to produce Bioactive Collagen Peptides® from the parent collagen protein. The process is similar to human digestion, however specific, so to consistently obtain the precise bioactive sequences.

Although gut digestion can break down collagen into peptides, the digestion is random and does not always cleave the collagen protein into the desired active sequences (Feng and Betti, 2017; Guo *et al*., 2015; Liang *et al*., 2014).

The Bioactive Collagen Peptides® by GELITA include a range of specific polypeptides of optimal molecular weight, containing circa 20-50 amino acid residues, which corresponds to 2-5 kDa in size (**Table 1**).

Table 1. GELITA's Bioactive Collagen Peptides® (BCPs) are optimized for specific health benefits

BCPs	Health benefit	Average molecular weight	Effective dose
VERISOL®	Skin, hair and nails	2 kDa	2,5 g
FORTIGEL®	Joints	3 kDa	5 g
FORTIBONE®	Bones	5 kDa	5 g
TENDOFORTE®	Ligaments and tendons	2 kDa	5 g
BODYBALANCE®	Body composition	3.5 kDa	15 g

How Bioactive Collagen Peptides® are absorbed by the gut

The ways in which Bioactive Collagen Peptides® can be absorbed intact through the gut wall are not completely elucidated. Paracellular transport seems to be the preferred route due to the narrower shape of the Bioactive Collagen Peptides® (<14Å) (**Figure 1**).

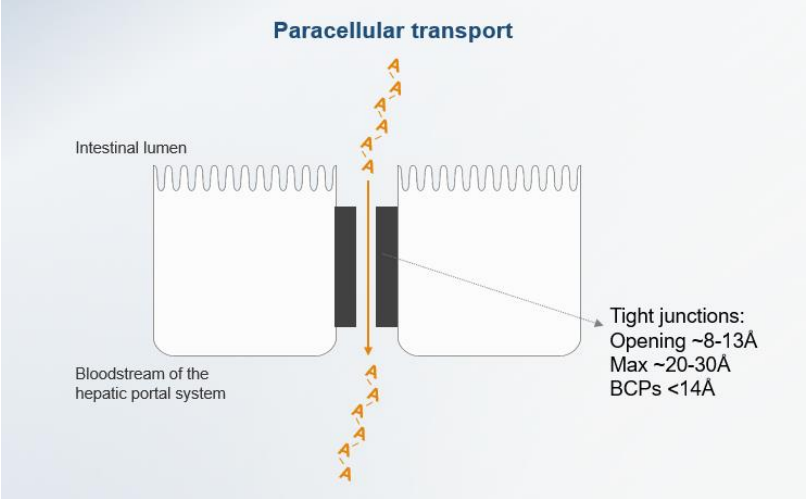
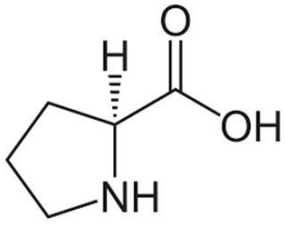


Figure 1. Paracellular transport of Bioactive Collagen Peptides® (BCPs) through the gut wall. The tight junctions, which are the areas in between the gut cells, form pores that normally allow the diffusion of small peptides (<600 Da). This also seems to be the preferred route for the absorption of BCPs, due to their narrower shape (<14Å) and resistance to hydrolysis. Adapted from: Srivastava 2017 p.457; Miner-Williams *et al.* 2014; Wada and Lönnerdal 2014 and Lorkowski 2012.

This may also be the case in situations when permeability is increased, such as during strenuous exercise (JanssenDuijghuijsen *et al*., 2016). Hence it might make sense to consume Bioactive Collagen Peptides®, ideally before and during physical activity, when used in association with an exercise or a physical rehabilitation program.

Specific characteristics support the intact absorption of Bioactive Collagen Peptides®

When collagen is denatured to produce Bioactive Collagen Peptides®, the single helix structure of the collagen type is maintained. This unique structure, formed by frequent Proline-Hydroxyproline-Glycine repeats, is more extended and narrower than a normal alfa-helix, so that it provides the favourable folding and stability that seem to facilitate gut absorption.



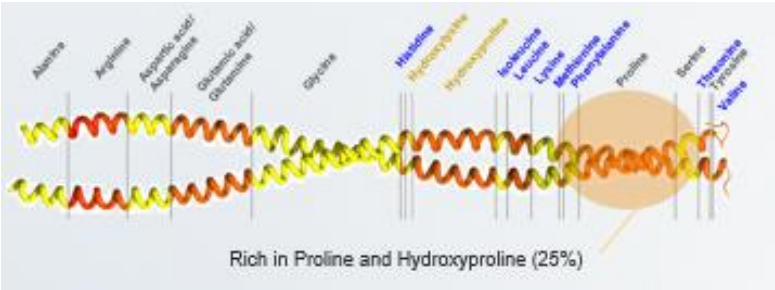
Proline

Proline, in particular, is the only cyclic amino acid and it forms kinks in the collagen polypeptide chain that are difficult to accommodate in typical globular proteins. This gives the Bioactive Collagen Peptides® a functional “drill” shape that is also resistant to hydrolysis (**Figure 2**).

Figure 2. The polypeptide chain analogy: spring vs. drill. The rare single helix structure of the collagen type is maintained in the Bioactive Collagen Peptides® (BCPs). A peptide chain is often interpreted as a linear string of linked amino acids. However, each amino acid has a slightly different shape that can significantly influence the final structure of the polypeptide. The unique Proline-Hydroxyproline-Glycine repeats in collagen gives BCPs a functional shape and resistance to hydrolysis, so that BCPs do not encounter the same permeability issues as the broader class of nutritional polypeptides.

Such unique characteristics differentiate Bioactive Collagen Peptides® from the broader class of polypeptides. Polypeptides that lack the correct folding have low and variable gut permeability, which is the case for the vast majority of polypeptides occurring in normal alfa-helix shape, as well as beta-sheets and random coils.

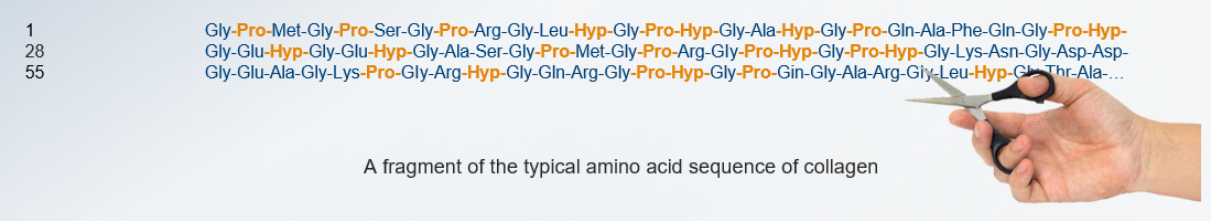
Interestingly, polypeptides that survive hydrolysis in the gut are usually those that are high in the amino acid Proline. Proline and Hydroxyproline represent ¼ of all the amino acids in collagen peptides, a remarkably high proportion not seen in any other protein source.



The importance of Proline in peptide activity has been best described by Tagliazucchi *et al*. (2016). In this study, one thing in common was observed for the peptides that resisted action of digestive enzymes: the peptides contained from one to four Proline residues in their sequence and, in many cases, had Proline at or near to the carboxylic end. They also found that these Proline-rich peptides were capable of slowing down the action of peptidases present in the intestinal brush-border membrane and in the colonic cells, further protecting the peptides from hydrolysis.

Proline is a key amino acid in the structure of peptides because it forms strong amino acid bonds that are resistant to the action of digestive enzymes, preserving the intact structure of Bioactive Collagen Peptides® during its fast passage through the gut (< ~1h).

In contrast, amino acids such as histidine – present in collagen only at ~1% – form weak peptide bonds that are more easily broken down by digestion. Bioactive Collagen Peptides® are less inclined to be disrupted by enzymatic activity in the gut because they lack in these weak points of hyper-hydrolysis.



A fragment of the typical amino acid sequence of collagen

In the pharmaceutical industry, for example, the new generation of “Cell-Penetrating Peptides” – called the ‘triple helical’ CPPs – are mimicking the native collagen folding in their structure for better stability against enzymatic breakdown and for a safer and more efficient route for delivery of active substances to the body (Lundquist and Artursson 2016; Shinde *et al*. 2015).

Optimal efficacy of Bioactive Collagen Peptides®

It is well-known that minimal differences in the amino acid sequence and protein structure can have a major impact, not only to the absorption of the polypeptides, but also on the stimulatory efficacy to the target cells.

This confirms the results of a series of preclinical trials performed by GELITA which have demonstrated that minimal differences in peptide molecular weight and structure ultimately have major effects on the efficacy of Bioactive Collagen Peptides® (**Figure 3**).

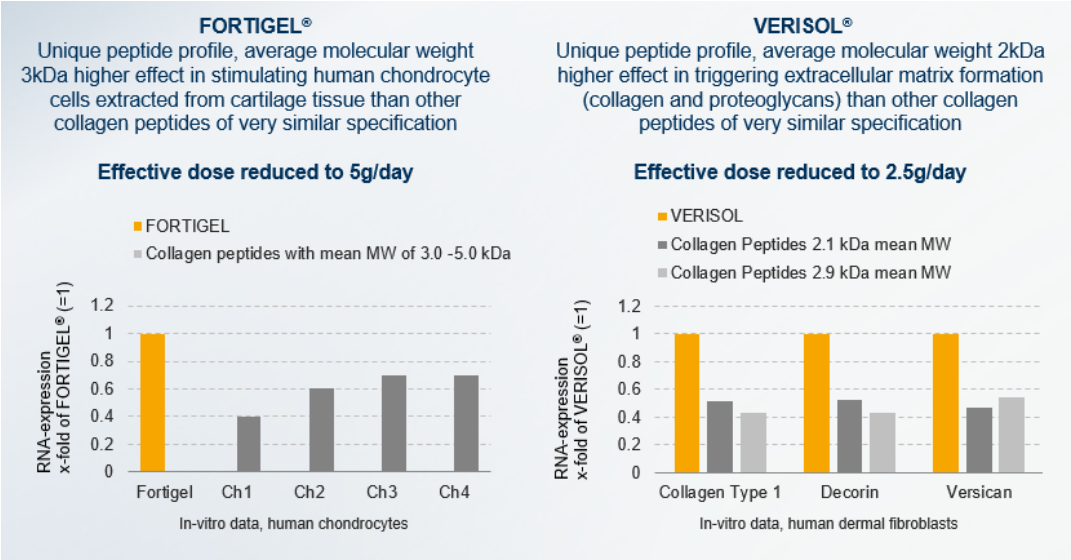


Figure 3. GELITA's preclinical trials with human connective tissue cells (internal reports)

Digestibility and bioavailability

The bioavailability of Bioactive Collagen Peptides® is excellent, with a true digestibility of 98.4% (Keith and Bell, 1998). The amino acids are important products of peptide digestion, as they are the protein building blocks of new connective tissue, once the target cells have been directly stimulated by the bioactive peptide fractions.

It is even more important that approximately 10% of the Bioactive Collagen Peptides® stay intact during digestion (good bioavailability) and are available for the stimulation of connective tissue cell metabolism.

It was demonstrated that Bioactive Collagen Peptides® appear in the blood stream and have an affinity for the family of connective-tissue cells (**Figure 4**) (Oesser *et al.* 1999).

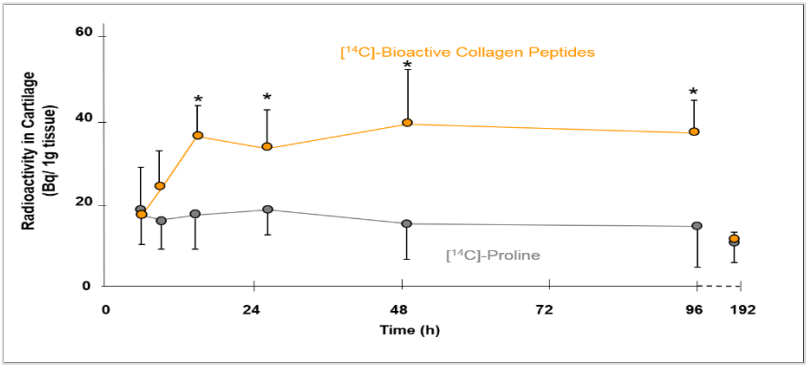


Figure 4. Bioactive Collagen Peptides® shows higher accumulation in cartilage tissue than the free amino acid Proline alone (animal model) (Oesser *et al.* 1999).

With regards to the mode of action of Bioactive Collagen Peptides®, it is discussed that specific peptides bind to certain receptors that are present on the surface of connective tissue cells (Siebert *et al.*, 2010). This seems part of a natural regulatory process which allows the cells to maintain their extracellular matrix and thus maintain the physiological functionality of the respective connective tissue.

Conclusion

The metabolism of food-derived peptides by the human body is a relatively new field and a great deal of new information is emerging every day to help us better understand the metabolism of food-derived peptides, especially of collagen peptides, for its unique characteristics. For this reason, this document is revised and updated yearly to include new information, so please always ensure that you hold the latest version.

On behalf of GELITA,

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