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# Brewer's Yeast (*Saccharomyces cerevisiae*) Hydrolysates Stimulate Cholecystokinin Secretion from the Enteroendocrine STC-1 Cells

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***Abstract***
***Background:*** *Previously we have shown that peptides derived from soybean β-conglycinin (BconP, BconB) stimulate cholecystokinin (CCK) secretion from the enteroendocrine cells (EECs) and suppress appetite in rats and in healthy human subjects. Later we found more potent peptides in legumes and pork meat proteins stimulate CCK secretion from the EECs and induce satiety in rats. Here we aimed to search new food peptides derived from other unconventional proteins which stimulate CCK secretion from the EECs.*
***Materials and Methods:*** *Brewer's yeast (BY, Saccharomyces cerevisiae) hydrolyzed with boiled water or food processing enzyme (pepsin) was examined for CCK-releasing activities from the EEC line STC-1. BY boiled water extracts (BW) were fractionated by acetonitrile (ACN) and treated with pronase to investigate active components.*
***Results and Discussion:*** *Brewer's yeast peptides stimulated CCK secretion dose-dependently which was greater than that of BconP, with the highest activity by BW despite of its low peptide content. Acetonitrile soluble fraction of BW (BWAS) stimulated CCK release, but insoluble fraction did not. Pronase treatment abolished the CCK-releasing activity of BW and BWAS.*
***Conclusion:*** *These results indicate that brewer's yeast boiled water extracts BW possess potent CCK-releasing activities and small to mid-sized peptides in BW are involved to stimulate CCK secretion in the EECs.*
***Keywords:*** *Saccharomyces cerevisiae, brewer's yeast protein, byproduct, pepsin, boiled water, hydrolysis, bioactive peptides, appetite, cholecystokinin, enteroendocrine cells, STC-1.*

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## I. Introduction

Searching for new food proteins and their peptides liberated after *in vitro* hydrolysis has become of growing interest due to abundant reports indicating that some specific peptide structures are biologically active with a variety of health benefits. These bioactive peptides may lead to the development of many functional food components [1-3]. The prevalence of lifestyle-related diseases such as obesity and diabetes has become an increasing problem around the globe. Hence, the development of functional food components may provide an opportunity for the prevention of these lifestyle diseases by reducing their risks through improved dietary practices in daily life. Subsequently, several antihypertensive, hypocholesterolemic, immunomodulatory, opioid, antioxidant and appetite-suppressive activities of many protein hydrolysates or peptides have already been determined [4-9].

The appetite-suppressive peptides induce satiety by stimulating cholecystokinin (CCK) secretion, a gut-brain satiety hormone from the proximal small intestine. CCK is secreted from the enteroendocrine I-cells in the lining of intestinal epithelium upon ingestion of nutrients [10-12]. It plays a leading role in stimulating pancreatic enzyme secretion, gallbladder contraction, inhibition of gastric emptying, and appetite suppression. In rats, an

elevation in CCK secretion has been shown to induce satiety after the gastric or duodenal delivery of peptones [13,14]. The sensory mechanisms by which these nutrients stimulate the EECs are still to be cleared and it is believed that the dietary protein-mediated CCK secretion is regulated by endogenous, trypsin-sensitive CCK-releasing peptides in the luminal protease-mediated feed-back mechanism [15]. However, some *in vivo* and *in vitro* studies found that dietary proteins and their peptides act directly on CCK-producing EECs to stimulate CCK secretion independent of endogenous CCK-releasing peptides [16-18]. The later investigations were further reinforced by the findings that peptones (peptic hydrolysates) stimulated CCK secretion in a CCK-producing murine enteroendocrine cell line, STC-1 [19-22].

Previously we have identified peptides in peptones (peptic hydrolysis) of soybean *β*-conglycinin and country beans (an unconventional legume) that stimulates CCK secretion with appetite-suppressive effects and later identified a satiety fragment (an arginine rich *β*51-63 peptide, VRIRLLQRFNKRS) from *β*-conglycinin followed by finding of more potent CCK-releasing peptides in dolicholin, a protein similar to *β*-conglycinin, but found in country beans [18,23-24]. There has been a world-wide trend to search for new food proteins and protein-derived functional food peptides from unconventional sources which remains as yet underutilized [25]. In line with these, due to our interests in developing appetite-suppressive and CCK-releasing peptides, we are also searching bioactive food peptides from alternative and underutilized food-stuffs with high protein contents.

Brewer's yeast (*S. cerevisiae*), originally a by-product of brewing, is an unconventional dietary component with an excellent source of proteins. It is relatively an inexpensive foodstuff which contains ~46% protein including many beneficial nutrients e.g. vitamins, minerals, nucleic acids, glutathione, amino acids, etc. and commonly known as a food supplement [26]. Studies have shown that brewer's yeast is an important supplement for those with type-II diabetes which can lower blood sugar levels and stimulate glucose metabolism [27-29]. Antihypertensive peptides with blood-pressure lowering effects and higher satiety effects of yeast proteins compared to other commonly edible proteins in animal models were also reported [26,30], however, the effects of yeast proteins or derivative peptides on CCK release have not yet been widely studied.

The aim of the present study was to search for new CCK-releasing peptides from brewer's yeast BY (*S. cerevisiae*), which is a major brewing byproduct. BY was hydrolyzed *in vitro* with boiled water or food processing protease pepsin (10 min and 60 min digestion) to compare their CCK-releasing efficacy with that of the known peptides in soybean *β*-conglycinin peptone (BconP) in the enteroendocrine cell line, STC-1, which has already been characterized as a suitable model for the study of CCK release [31-33].

## II. Materials And Methods

### *Materials*

BY-G brewer's yeast from *S. cerevisiae*– a brewer's yeast removed hop resinous bitter substance with alkaline treatment was provided by Kirin Brewery Co., Ltd. (Tokyo, Japan). The chemical composition of BY (BY-G) is already known [26]. Purified soybean *β*-conglycinin flour was a gift from Fuji Oil Co., Ltd. (Osaka, Japan). All chemicals used were obtained from Wako Pure Chemical Industries Ltd., Osaka, Japan unless otherwise noted.

### *Preparation of Brewer's Yeast Boiled Water Extract*

Since BY-G is water-insoluble, BY-G powder (10 g) was strongly homogenized in water (200 mL) for 5 min using a Polytron homogenizer (Kinematica, Lucerne, Switzerland). Briefly, the homogenate was adjusted to pH 7.0, boiled (100°C) for 60 min, centrifuged at 3,750 *g* to get supernatant and then lyophilized to produce brewer's yeast BY boiled water extract (BW).

### *Preparation of Brewer's Yeast Peptones with Pepsin*

Pepsin hydrolysis was performed as previously described with slight modifications [18]. Briefly, brewer's yeast BY powder or soybean *β*-conglycinin flour (10 g each) was suspended in phosphate (200 mL) and strongly homogenized. They were then treated with pepsin (10,870 units/g substrate, Sigma Aldrich, St. Louis, MO) at pH 1.8, 37°C for 10 min followed by immediate boiling, neutralization and desalting with $Ca(OH)_2$, centrifugation at 3,750 *g* and lyophilization of the supernatant. The peptones obtained are designated as brewer's yeast BY peptone (P10) and soybean *β*-conglycinin peptone (BconP), respectively. Another peptone labeled as BY peptone (P60) was obtained as described above except the difference in time-course for pepsin hydrolysis for 60 min.

The peptide content of the prepared test hydrolysates was determined by the method of Lowry [34] using bovine serum albumin (BSA) as a standard and expressed as the peptide purity (%) against BSA. These hydrolysates were studied to identify their CCK-releasing activities from the CCK-producing murine enteroendcrine cell line STC-1.

***Separation of Active Peptides in Brewer's Yeast Boiled Water Extract (BW) with Organic Solvents***

BW was separated into soluble and insoluble fractions by the addition of cold acetonitrile (ACN) up to 50% (final conc.) on ice for more than 30 min. The resulting supernatant and precipitate were separated following centrifugation at 1050 *g*, 4°C for 15 min and freeze-dried as the BW acetonitrile soluble fraction (BWAS) and BW acetonitrile insoluble fraction (BWAI). The recovery yield of BWAS was ~70% and BWAI was ~25%.

***Digestion of Active Peptides in Brewer's Yeast Boiled Water Extract (BW) with Pronase***

Pronase digestion of boiactive peptides were performed as already described [24]. Briefly, dissolved BW or BWAS (100 mg in 20 mL, pH 7.0) was treated with the protease pronase at 225 PUK (proteolytic unit/g substrate, Pronase Protease, *Streptomyces griseus*, Calbiochem, EMD Biosciences Inc., La Jolla, CA) for 60 min at 37°C. The reaction was stopped by boiling and the pronase-treated BW or BWAS was freeze-dried after re-adjustment to pH 7.0.

***Cell Culture and Study for CCK-Releasing Activities***

STC-1 cells were kindly provided by Dr. D. Hanahan (University of California, San Francisco, CA). These cells were originally derived from an intestinal endocrine tumor obtained from double transgenic mice [35]. STC-1 cells were grown in Dulbecco's modified Eagle's Medium (DMEM; 4.5 g/L glucose, with L-glutamin, without sodium pyruvate; GIBCO BRL 12100-038, Grand Island, NY) containing 10% fetal calf serum, 100 U/mL penicillin, and 100 µg/mL streptomycin under a humidified 5% $CO_2$ atmosphere maintained at 37°C. Cells between passage 30 and 40 were used at 80-90% confluence.

For secretion studies, $1.25 \times 10^5$ cells were seeded into 48-well plates and used when they reached sub-confluence after culturing for 2-3 days. The cultured cells were then washed twice with HEPES buffer (140 mM NaCl, 4.5 mM KCl, 20 mM Hepes, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 10 mM Glucose, pH 7.4) and test hydrolysates dissolved in HEPES buffer (1-5 mg/mL solid) were added to the wells. HEPES buffer without hydrolysate was added as negative control (Control). After incubation for 60 min at 37°C in the $CO_2$ incubator, the medium was collected on ice, centrifuged at 850 *g* at 4°C for 5 min to remove cells and the supernatant was stored at -50°C until CCK measurement. The released CCK was measured by a commercially available enzyme immunoassay kit (Phoenix Pharmaceuticals, Inc., Belmont, CA, USA).

***Calculations and Statistical Analysis***

Results of the CCK secretion study are expressed as concentrations of CCK (pM) in the supernatant after incubation with or without hydrolysates or stimulants. All results of CCK secretion study are expressed as means ± SEM and analyzed with one-way ANOVA followed by Duncan's multiple range test ($P < 0.05$).

## III. Results

The peptide content of the test hydrolysates (BconP, BW, P10, P60) has shown in Table 1. The results show highest peptide content (84%) in BconP (soybean $\beta$-conglycinin peptone, a known source of CCK-releasing and appetite-suppressive peptides). BY peptones P10 and P60 shows a moderate peptide content of 31% and 34% respectively, while the BY boiled water extract BW had an exceptionally low peptide content (only 15%) among the test hydrolysates.

**Table 1**. Peptide content of the test hydrolysates prepared for screening their CCK-releasing activities.

| Test hydrolysates | Label | Peptide content (%) |
|---|---|---|
| Soybean $\beta$ -conglycinin peptone | BconP | 84 |
| Brewer's yeast (BY) boiled water extracts | BW | 15 |
| BY peptone (10 min hydrolysis) | P10 | 31 |
| BY peptone (60 min hydrolysis) | P60 | 34 |
| BW ACN soluble fraction | BWAS | 18 |
| BW ACN insoluble fraction | BWAI | 13 |

BY hydrolyzed with pepsin for 60 min (P60, 34% peptide) produced a higher CCK-releasing activity than did BconP at 5 mg/mL conc. (Figure 1). BY hydrolyzed with pepsin for 10 min (P10, 31% peptide) and BY boiled water extract (BW, 15% peptide) also produced similar activities at 5 mg/mL conc., as did BconP (84% peptide, a positive control) in the stimulation of CCK-release. The stimulation in CCK-release by brewer's yeast BW, P10 and P60 was dose-dependent (1mg/mL vs 5 mg/mL conc.) with similar activities at 5 mg/mL conc., however, BW showed the similar CCK-releasing activity despite of its low peptide content (Figure 1, Table 1).

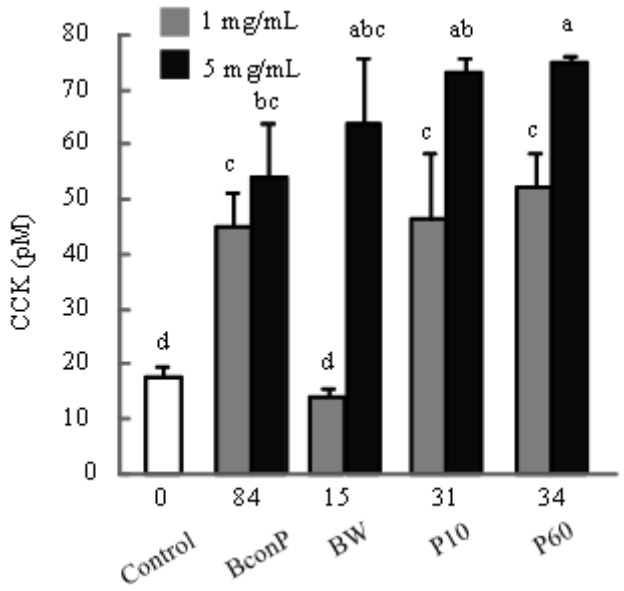


**Figure 1.** CCK-releasing activity after exposure to soybean *β*-conglycinin peptone (BconP, a positive control), brewer's yeast boiled water extract (BW), brewer's yeast peptone (P10) and brewer's yeast peptone (P60); at 1 and 5 mg solid/mL. Numbers depicted below the respective bars denote peptide content (%) as determined by Lowry's protein assay except for the Control which contained no peptide. Values are means ± SEM of 3 repeated measurements. Means without a common letter are significantly different ($P < 0.05$).

The result that the brewer's yeast boiled water extract BW produced a higher CCK-releasing activity despite of its lowest peptide content provided us the foundation for further characterization of the yeast peptides in BW. The CCK-releasing activity of the BY boiled water extracts (BW) fractionated by acetonitrile (ACN) has shown in Figure 2. Both BW and its ACN -soluble fraction (BWAS) stimulated CCK-secretion dose-dependently; however, the ACN -insoluble fraction (BWAI) failed to stimulate the activity from the cells. BWAS stimulated CCK-release but this stimulation was less than the activity produced by BW, despite of their similar peptide content (Table 1).

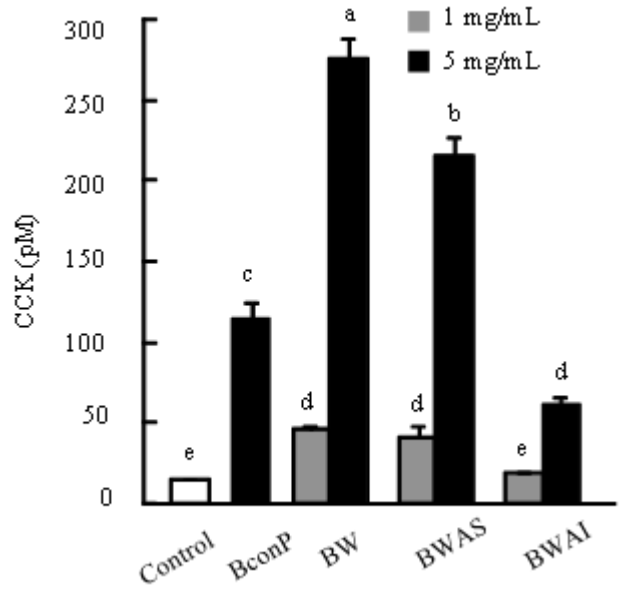


**Figure 2.** CCK-releasing activity after exposure to soybean *β*-conglycinin peptone (BconP, a positive control), brewer's yeast boiled water extract (BW), brewer's yeast boiled water extract acetonitrile-soluble fraction (BWAS) and brewer's yeast boiled water extract acetonitrile-insoluble fraction (BWAI) for 60 min at 1 and 5 mg solid/mL, the Control contained no peptide. Values are means ± SEM of 3 repeated measurements. Means without a common letter are significantly different ($P < 0.05$).

To confirm that the CCK-releasing activities of the brewer's yeast boiled water extracts are derived from peptides, BW and BWAS was treated with pronase to destroy the peptide structures. The CCK-releasing activity of BW and BWAS "with" or "without" a prior pronase treatment has shown in Figure 3. The result shows that both the BW and BWAS pre-treated with pronase abolished the CCK-releasing activities.

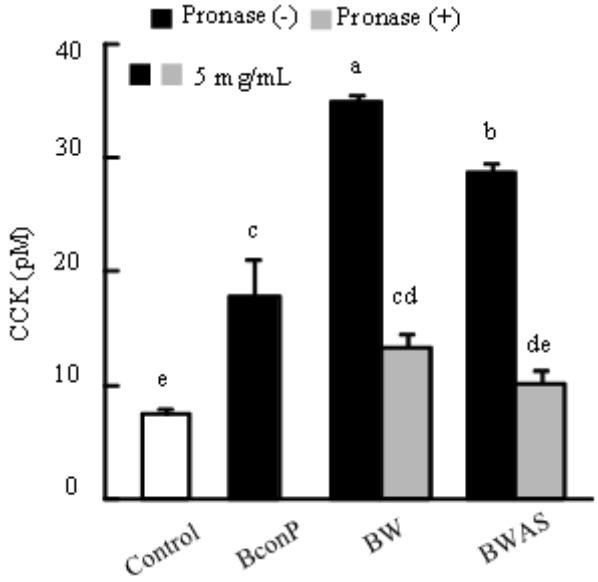


**Figure 3.** CCK-releasing activity after exposure to soybean *β*-conglycinin peptone (BconP, a positive control), brewer's yeast boiled water extract (BW) and brewer's yeast boiled water extract acetonitrile-soluble fraction (BWAS) "with (+)" or "without (-)" pronase treatment, for 60 min at 5 mg solid/mL, the control contained no peptide. Values are means ± SEM of 3 repeated measurements. Means without a common letter are significantly different ($P < 0.05$).

## IV. Discussion

The aim of the present study was to explore brewer's yeast peptides extracted from brewer's yeast, an unconventional and underutilized source of protein as a byproduct. The peptides were obtained by hydrolysis with food-processing protease pepsin (peptones P10 and P60) or extracted with boiling water (BW, without any protease digestion) in order to search for new CCK-releasing peptides. BY hydrolysates digested with pepsin (P10, P60) stimulated CCK secretion. However, unexpectedly boiled water extract BW (having 15% peptide content) produced similar activities as did BconP (84% peptide, a positive control) which has already been reported as a potent CCK-releasing and appetite-suppressing peptide (Figure 1, Table 1) [18,23]. In fact, all of the brewer's yeast extracts, especially BW produced similar or higher CCK-releasing activities than did BconP even with an extremely low peptide content.

Several studies including ours already have shown that peptones from both animal and plant origins were able to stimulate CCK secretion in the EECs (18, 20-24). Previously we identified specific peptide structures in peptones of soybean *β*-conglycinin involved in the induction of satiety through CCK release and later shown more potent CCK-releasing peptones in country beans, a closer legume to soybean as already mentioned [23,24]. The present results demonstrate that brewer's yeast boiled water extract BW and peptones (P10, P60) are effective to liberate specific peptide structures to trigger active CCK-releasing properties and that the BW peptides are the most potent in stimulating CCK secretion in the EECs (Figure 1). These results also suggest that all the brewer's yeast hydrolysates contain putative peptide structures despite of their lower peptide contents and, therefore possess higher biological activities than that of BconP in potentially inducing CCK secretion from the EECs.

BW showed a moderate stimulation in CCK-release despite of its exceptionally low peptide content (15%), which was prepared without any enzymatic hydrolysis. This screening provided us with the ground for further characterization of brewer's yeast peptides in BW. The components in BW were separated into ACN-soluble fraction (BWAS) and ACN-insoluble fraction (BWAI). The ACN-soluble fraction BWAS triggered the CCK-releasing activity significantly whereas the ACN-insoluble fraction (BWAI) has failed to stimulate the secretion from the EECs suggesting mid-size or small peptides in BWAS are responsible for the activity (Figure 2). However, still a higher CCK-releasing property is observed in BW than that in BWAS despite of their similar peptide content (Table 1). There is a possibility that the ACN treatment denatured some of the active peptides in BW. It is also plausible that unlike peptides in BWAS, peptide(s) with relatively higher molecular size

correspondingly responsible with small to mid-size peptides in BW for its higher activity than that of BWAS. Future studies must be taken to characterize these active biomolecules for CCK-release.

To determine whether the CCK-releasing activity in BW and BWAS depends on peptides, they were treated with pronase to destroy peptide structures. Pronase, a non-specific potent protease, digest proteins or peptides into single amino acids. Previously, we have reported that specific peptide structures derived from several dietary proteins and a peptide with multiple arginine residues in BconP is a pre-requisite for inducing CCK secretion [8,21,23,24]. However, single amino acids are also shown to stimulate CCK secretion in the STC-1 cells by us and others [36,37]. The result of both the BW and BWAS pre-treated with pronase abolished the CCK-releasing activity confirms that the activity originates from peptide(s) rather than in free amino acids or other components in BW and BWAS (Figure 3).

It has been shown that brewer's yeast proteins can enhance satiety more efficiently than other commonly edible proteins in animal models [30]. Here we have shown that small to mid-sized peptides in BW and BWAS are potently involved in CCK secretion rather than free amino acids, to trigger CCK secretion in the EECs. The stimulatory mechanisms by which different dietary proteins and liberated peptides act to mediate CCK secretion that promote satiety has to be unraveled in future studies.

## V. Conclusions

In summary, we have demonstrated that the peptic (P10, P60) and boiled water (BW) hydrolysis of brewer's yeast, an unconventional and underutilized protein byproduct, is effective to liberate peptide molecules to stimulate CCK secretion in the intestinal endocrine STC-1 cells and, BW small to mid-sized peptides are the most potent in stimulating CCK secretion from the EECs. This finding would benefit the by-product to develop as a unique future functional food component. Further studies are needed to characterize and identify the active peptide(s) involved in the enhancement of CCK release, examine satiety through screening appetite-regulatory activities of BW in animal models (*in vivo*) and in healthy human subjects (clinical).

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