Peptides that Regulate Food Intake
Cholecystokinin and stomach distension combine to reduce food intake in humans

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Kissileff, Harry R., Julie C. Carretta, Allan Geliebter, and F. Xavier Pi-Sunyer. Cholecystokinin and stomach distension combine to reduce food intake in humans. Am J Physiol Regul Integr Comp Physiol 285: R992–R998, 2003. First published August 14, 2003; 10.1152/ajpregu.00272.2003.—The aim of this study was to test the hypothesis that gastric distension can enhance the effect of cholecystokinin (CCK) on reduction of food intake in men and women. Eight normal-weight subjects of each gender were tested four times each with either CCK or saline infusion crossed with gastric distension or no distension. Intravenous infusion of a low dose of CCK octapeptide (CCK-8; 112 ng/min for 23 min) combined with a subthreshold gastric distension induced by a water-filled balloon (300 ml) resulted in a significant (means ± SED: 191 ± 61 g in men, 209 ± 61 g in women, and 200 ± 43 g combined) reduction in intake of a liquid meal compared with saline infusion and unfilled gastric balloon. This combined effect was the result of a large and significant CCK effect when the stomach was distended (CCK vs. saline with distension: 169 ± 43 g) and a small and insignificant distension effect (distension vs. no distension without CCK: 31 ± 43 g). The CCK effect alone on intake (CCK vs. saline) without distension was not significant in men (72 ± 61 g) but was significant in women (121 ± 61 g). These results are consistent with the hypothesis that CCK’s suppression of food intake is enhanced when the stomach is distended.

satiety; feeding; gastric distension

Cholecystokinin (CCK), a peptide hormone released by the duodenum mainly in the presence of digestion products of fats and proteins (5), reduces food intake in a variety of species, including humans (see Ref. 21 for a review). Physiologically, CCK stimulates pancreatic enzyme secretion (8), induces gall bladder contractions (1), increases neural activity in the gastric vagal afferents (18), relaxes the stomach, constricts the pylorus (13, 20), and inhibits gastric emptying when food is in the stomach (2, 12), thereby increasing gastric distension.

It has been suggested that the increased gastric distension induced by slowing of gastric emptying may be the mechanism by which CCK reduces food intake (15). In support of this hypothesis, Moran and McHugh (15) reported that in monkeys a saline preload was necessary to decrease food intake after a low dose of CCK. In humans, Murrahainen et al. (17) demonstrated that intake of a test meal was significantly lower when CCK octapeptide (CCK-8) was given after a 500-g but not a 100-g soup preload. Without both CCK and the larger preload, no significant decrease in intake was observed. CCK infusion significantly decreased gastric emptying and thereby increased the gastric volume remaining after subjects ingested 500 g of soup. The size of the gastric volume increase after CCK was 80 g (from 230 to 310 g) after 25–30 min (end of ad libitum meal) compared with saline infusion (16). However, the reduction in gastric emptying also reduced the amount of nutrients entering the intestine. Therefore, the question was which of the stimuli provided by the soup (i.e., gastric distension or nutrient stimulation, of the intestine or both, or even the additional oral stimulation) produced by the preload combined with CCK to enhance CCK’s food intake-reducing effect.

To begin answering this question, the current experiment was conducted to examine the effects of a non-nutritive increase in gastric volume on food intake after administration of CCK-8 or saline. Demonstration of an interaction between CCK and gastric distension would support the previously advanced hypothesis (14, 17) that CCK amplifies signals of gastric distension, which contribute to satiation.

Two previous results guided selection of levels of distension and CCK that were used in the present study. First, Geliebter et al. (4) showed that different volumes of gastric distension induced by filling a balloon with water in the stomachs of men and women significantly reduced food intake only when gastric distension exceeded 400 ml. The average intake-reducing efficiency was 40%, suggesting that although distension contributes to satiety, it cannot account for it entirely. Because the results from Geliebter et al. (4)
suggested that 400 ml was the threshold volume for reducing intake, a subthreshold volume of 300 ml was used as the high volume to maximize the possibility of detecting a supra-additive interaction. In the present experiment, a low dose of 112 ng/min of CCK was used, based on the finding that twice this level of CCK, compared with saline, reduced intake only when a 500- but not a 100-g preload was given (17). Two predictions were made. First, subjects would consume less after 300 ml of distension and an infusion of CCK together than after any of the other conditions (i.e., the combined effect of distension and CCK would be significant). Second, neither CCK alone nor distension alone would significantly reduce intake. If the combined effect was sufficiently large, these predictions should give rise to a significant distension by CCK interaction (CCK vs. saline, with distension; CCK vs. saline, without distension).

METHODS

Subjects. Eight nonobese male and eight nonobese female volunteers were recruited by means of a college newspaper advertisement and flyers posted in the surrounding area. The number of subjects was originally planned to be twelve for each sex but was reduced to eight when statistical significance was achieved and because it was difficult to recruit subjects for this invasive protocol. Subjects met the following criteria: 1) weight within 15% of the desirable weight for height [body mass index (BMI) between 19 and 23.8]; 2) age between 18 and 35 yr; 3) nonsmoker; 4) no active medical problems; 5) taking no medications (except for regular vitamin/mineral supplements); 6) no allergies, including food allergies; 7) no history of weight problems; and 8) unrestrained eaters ( restraint score <10 on the Stunkard and Messick restraint scale; see Ref. 22). In addition, they provided a short medical history and a physical examination to ensure good health. They were screened by eating tests that eliminated any candidates who did not like the test meal food and would not eat a sufficient amount of it to be considered a meal. These procedures were approved by the Institutional Review Board on Human Experimentation at St. Luke’s/Roosevelt Hospital Center, and informed consent was obtained from all participants. During the screening, the participants were required to 1) rate the test meal food (see Design and daily procedures) at least six on a nine-point scale of liking either during the taste test, conducted on the first screening session, or after eating it as a meal; 2) eat all of the standardized breakfast (see Design and daily procedures); and 3) consume at least 250 g of the test meal on either the first or second screening day.

Demographics. The demographic characteristics of the participants were as follows: for men (means ± SD), age 25.7 (±2.4) yr, height 1.79 (±0.04) m, weight 71.8 (±5.3) kg, BMI 22.3 (±1.6), and restraint score 5.6 (±2.6); and for women, age 23 (±3) yr, height 1.65 (±0.07) m, weight 59.03 (±6.76) kg, BMI 21.71 (±1.96), and restraint score 3 (±2).

Initial instructions to subjects and rating sheets. Subjects were given a written description of the study, which indicated that its purpose was to determine the effects of a balloon filled in their stomach to reactions on subsequent food consumption. They were told that both a balloon and an intravenous catheter (IV) would be inserted every session, and that on different days either a protein or saline would be infused. They were also informed that no unusual side effects were to be expected from either the balloon or the infusion. The subjects were not told that food intake was being measured, because this information could potentially influence a subject’s eating behavior. To reinforce the initial description of the purpose of the study and to divert attention away from the main variable of interest (food intake), subjects were asked to fill out questionnaires during each session and at the end of every trial. The questionnaires administered during each session used a 150-mm visual analog scale (VAS) anchored on the left-hand side by the words “Not at all” and on the right by “Extremely.” The questions included “How hungry do you feel right now?” (hereafter referred to as “hunger”), “How full do you feel right now?” (full), “How sick do you feel right now?” (sick), and “How much stomach discomfort do you feel right now?” (discomfort). After the last question, there were two blank spaces for subjects to fill in any other sensations that may have been experienced during the session and a scale beneath each to rate it. The questionnaire administered at the end of each trial (postmeal questionnaire) contained questions about the acceptability of the meal, taste, and the satiating effect of the meal.

Design and daily procedures. The experiments were conducted in a specially constructed eating room with approximate dimensions of 11 ft × 5 ft, similar to a room previously described in detail (see Ref. 9). Subjects were tested six times. The first two sessions were used for screening/adaptation, and the remaining four sessions served as experimental trials. The first session was used for three purposes: to determine 1) whether the subject liked the test meal, 2) whether the subject would eat enough of it to be considered a meal, and 3) whether the subject could adapt to consuming the meal with a tube in the stomach. The second session was used to further adapt the subject to the procedure so neither the IV nor the balloon would inhibit normal intake. Methods on all days were identical (see Fig. 1), with the exceptions that on the first and second days the balloon was filled to 100 ml, saline was administered on both trials, and a taste test was given before the breakfast on the first session. Each subject reported to the laboratory after an overnight fast, at which time he or she was given a standardized 300-kcal breakfast consisting of one Thomas English muffin (S.B. Thomas, Totowa, NJ) with 1.5 pats (7 g) of Land O’Lakes butter (Land O’Lakes, Arden Hills, MN) and 249 g of natural-style apple juice (Red Cheek; Cadbury Beverages, Stamford, CT). The subject was instructed to eat the entire muffin and drink all of the juice before leaving the laboratory. All subjects complied with this request on every trial. After breakfast, the subject was instructed not to eat or drink anything except water before returning to the laboratory again 2.5 h later.

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Experimental Procedure</th>
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<tr>
<td>-150</td>
<td>Breakfast</td>
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<tr>
<td>-15</td>
<td>I.V. Started</td>
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<tr>
<td>0</td>
<td>Start Balloon Filling</td>
</tr>
<tr>
<td>10</td>
<td>Stop Balloon Filling</td>
</tr>
<tr>
<td>30</td>
<td>Start Meal</td>
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<tr>
<td>40</td>
<td>End Meal</td>
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Fig. 1. Time line of experimental procedures and giving of rating sheets. Times are in min. IV, intravenous catheter; Q, questionnaire.
The procedures for balloon insertion were similar to those previously reported (3). When the subject returned for the lunch meal, instructions for the afternoon session were given by means of a prerecorded tape (2 min, 10 s). If a subject had any questions, he/she was provided with an answer after the tape recording had terminated. Afterward, a 20% benzocaine solution (Hurricane, Beutlich Pharmaceuticals) was sprayed for 5 s to anesthetize the back of the throat. A thin latex balloon (Trojan plain-end nonlubricated condom, shortened to 4 in, with a capacity of 8,000 ml) attached to a double-lumen tube (Salem Sump, 10 Fr) was then passed orally into the stomach. The tube exiting the mouth was secured to the side of the subject’s cheek to prevent obstruction of the gastroesophageal junction. The distance from the gastroesophageal sphincter to the mouth was estimated as the sum of the distances from the mouth to the ear lobe and the ear to the sternum. This estimation was used as a guide for insertion of the balloon into the stomach. The tube exiting the mouth was then temporarily taped to the subject’s cheek to facilitate comparisons with previously reported results (3). When the subject returned for the next scheduled experimental session, intake was determined by percentage of calories was 12.8% protein, 67.4% carbohydrate, and 20.2% fat (1.04 kcal/g). Subjects were instructed by a tape-recorded message (1 min, 30 s) to consume the shake as they would a normal meal and, when they were finished, to signal the researcher by placing the straw from the shake on a remote sensory holder. At the time the recorded message terminated and the subject began eating, the experimenter, watching the subject on a closed circuit video monitor in a control room, noted meal onset time and continued to observe the subject to assess meal duration and compliance with instructions. If a subject failed to comply with the instructions (e.g., disposed of food, handled the balloon, or engaged in other activities while eating), his/her data for that day were not used and the session was repeated. All subjects complied with the instructions on every trial.

Five minutes after the subject indicated he/she had finished eating, he/she was asked to fill out the seventh questionnaire. The balloon was then emptied at the same rate and with the same procedures used during filling. The subject was then instructed to fill out the seventh questionnaire before the balloon was removed by retracting the double-lumen tube. Once the balloon was removed, the IV was taken from the subject’s arm, and he/she was asked to fill out the postmeal questionnaire. When the subject finished the questionnaire, he/she could leave after being reminded not to eat or drink anything except water after midnight before the next scheduled experimental session. Intake was determined by difference in meal weight as well as intake recorded by the eating monitor.

Design and analysis. For the last four trials (test sessions) of the experiment, subjects were assigned to one of four Latin square sequences of the peptide (CCK or saline) and distension (balloon filled or unfilled). The four sequences (e.g., ABCD, BCDA, DBAC, and CBDA, where CCK filled is A, CCK unfilled is B, saline filled is C, and saline unfilled is D) were counterbalanced for the eight subjects so that each sequence was given to two subjects. Only data from the test sessions were analyzed statistically, because only those days were counterbalanced for treatments and sequence effects. Initially, a one-way analysis of variance (ANOVA) with subject, trial, and treatment condition as factors was used to assess the reliability of the differences obtained during distension-peptide combinations for both food intake and meal duration. Because the trial effect was not significant, it was pooled with the error term. Intakes were analyzed by means of a two-way mixed model (sex as the between and treatment as within). Treatment was considered to be a single variable at four levels, two levels of distension (0 and 300 ml) crossed with two levels of infusion (CCK and saline). Ratings were analyzed by means of a three-way mixed-model ANOVA that was identical to the two-way model but with an added within-group factor of the period at seven levels. Planned comparisons among treatments (see RESULTS and Table 1 for specific list of comparisons) were made for each sex, separately, to facilitate comparisons with previously reported results in which nutrients were combined with CCK (17). The same comparisons were also made for both sexes together. For

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Table 1. Intake and duration effects (mean contrasts with relevant control)

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<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Together</th>
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<tbody>
<tr>
<td><strong>Intake, g</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Combined effect of distension and CCK</td>
<td>191†</td>
<td>209†</td>
<td>200§</td>
</tr>
<tr>
<td>2) CCK effect at 300-ml distension</td>
<td>162‡</td>
<td>176‡</td>
<td>168§</td>
</tr>
<tr>
<td>3) CCK effect with no distension</td>
<td>72</td>
<td>121‡</td>
<td>96*</td>
</tr>
<tr>
<td>4) Distension effect without CCK</td>
<td>29</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>5) Distension effect with CCK</td>
<td>120§</td>
<td>89</td>
<td>104*</td>
</tr>
<tr>
<td>6) Interaction (effect 2 – effect 3)</td>
<td>91</td>
<td>55</td>
<td>73</td>
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| **Duration, min**         |           |           |           |
| 1) Combined effects of distension and CCK | 1.73‡      | 1.11*      | 1.42§      |
| 2) CCK effect at 300-ml distension       | 0.57      | 0.95       | 0.76*      |
| 3) CCK effect with no distension          | 1.10*     | 0.55       | 0.82*      |
| 4) Distension effect without CCK          | 1.16*     | 0.16       | 0.66       |
| 5) Distension effect with CCK             | 0.63      | 0.56       | 0.60       |
| 6) Interaction (effect 2 – effect 3)      | -0.53     | 0.40       | -0.06      |

Mean differences are as follows: (1) between saline nondistension condition and cholecystokinin (CCK) 300-ml distension condition; (2) between CCK and saline treatments accompanied by 300-ml distension; (3) between CCK and saline treatments accompanied by no distension; (4) between no distension and 300-ml distension accompanied by saline; (5) between no distension and 300-ml distension accompanied by CCK. SE of difference for men and women = 61 for intake effects 1–5 and 86 for effect 6 and 0.51 for duration effects 1–5 and 0.72 for effect 6. SE of difference for the sexes combined = 43 for intake effects 1–5 and 61 for effect 6 and 0.36 for duration effects 1–5 and 0.51 for effect 6. *P < 0.05, †P < 0.01, ‡P < 0.005, §P < 0.001.

Comparisons among treatments within each sex, a pooled between- and within-subjects error term was used (23). The SAS statistics package (v. 8.0 for personal computers) was used for all statistical analyses. In all analyses of intake and duration, a probability of 0.05 was accepted as statistically significant. For the questionnaires, the Bonferroni procedure (7) was used to adjust the significance level of the questionnaire data (7 time periods of interest), and significant differences between conditions are only reported if their adjusted values were 1–10(1–α/1–α0.05), where α0.05 is the unadjusted conventional level of 0.05 and N is the number of time periods × number of questions (7 x 4 = 28).

RESULTS

Intake. There was a significant difference among the four treatment conditions for men ($F_{3,21} = 4.83, P = 0.01$), women ($F_{3,21} = 3.94, P = 0.022$), and both sexes together ($F_{3,42} = 8.45, P = 0.0002$) but no sex effect ($F_{1,14} = 2.07, P = 0.172$) and no sex × treatment interaction ($F_{3,42} = 0.13, P = 0.938$). Table 1 shows the important comparisons, and Fig. 2 shows means for men and women separately and together, along with their least significant differences within subjects. The main results (keyed by no. to Table 1) were as follows. 1) The combination of CCK and distension of 300 ml reduced food intake by a mean of 200 g (191 g in men, 209 g in women) compared with the saline nondistension condition. 2) CCK reduced intake significantly when the stomach was distended (by the balloon) by a mean of 169 g (162 g in men, 176 g in women). 3) However, without distension, CCK did not significantly reduce intake in men but did significantly reduce intake by 121 g in women and in both sexes together by 96 g. 4) Distension alone (i.e., without CCK) had little effect (mean of 31 g). 5) In contrast, during CCK infusion, intake was significantly lower after distension compared with nondistension by 120 g in men but was not significantly lower (89 g) in women. This is the one contrast in which men and women differed, although the difference between them was not significant. 6) Because CCK combined with (but not without) distension significantly reduced intake, CCK enhanced the distension effect by an average (over both sexes) of 73 g (i.e., the CCK effect was 73 g greater with than without distension). However, this interaction effect was not significant in either sex alone or in the two sexes together.

Meal duration. Analysis of variance showed a significant difference among treatments ($F_{3,21} = 3.36, P = 0.038$) for meal duration for men. The pattern of differences in the planned comparisons was different for duration than for intake, so we shall describe it independently (see Table 1 for details) and point out similarities and differences. 1) Similar to the results with intake, meal duration was reduced significantly by CCK combined with 300 ml of distension in both men (by 1.73 min) and women (1.11 min), with a mean reduction of 1.42 min for the two sexes together. 2) CCK reduced meal duration significantly when the stomach was distended (by the balloon) by a mean of 0.76 min with the sexes together (as it did for intake), but the reduction was not significant in either sex alone (unlike intake). 3) Unlike intake, meal duration was reduced more (and significantly) in men than in women (not significant) by CCK without distension. However, without distension, CCK reduced duration significantly, as it did intake, by 0.82 min. 4) Distension alone (i.e., without CCK) reduced meal duration in men (unlike intake) but not in women and not in both sexes together (similar to intake). 5) Distension with CCK resulted in no significant reductions in duration, probably owing to the large and significant reduction by CCK alone. This result was similar to the result for intake only in the women. 6) The interaction between CCK and distension was not significant, just as it was not for intake. 7) The main effect of CCK was a significant reduction in meal duration, just as in intake, in both sexes separately and together. 8) But the main effect of distension was only significant in the men (unlike intake) and both sexes together (as with intake).

VAS ratings. There were two significant differences in ratings (see Fig. 3). 1) After the balloon was fully filled and before the CCK infusion had begun, men and women together (but not separately) averaged over both infusion conditions rated feeling significantly more “full” (21.65 mm ± 6.56 SED, $t_{350} = 3.3$; unadjusted $P = 0.001$, adjusted $P < 0.05$) than when the balloon was not filled. 2) Five minutes after completing the meal, men and women together (but not separately) reported significantly more of a “sick” feeling
Fig. 2. Mean intakes and meal durations for each experimental treatment by sex [B: females (n = 8); C: males (n = 8)] and for both sexes together (A). Error bars to right of plots show least significant differences (LSDs; LSD = \sqrt{n \times MSE_{within} \times t_{(a)}}) within subjects for comparisons between any 2 experimental treatments. Error bars to left of plots show between subjects (MSE_{between} \times t_{(a)}) for comparing 2 means between sexes for a particular experimental condition. Variation for individual means is not shown because the 2 LSDs within and between provide information needed for any comparison. Any contrast larger than the corresponding LSD is significant. Points with different letters are significantly different.
The main results for the genders together showed a significant reduction in intake after a combination of CCK and distension, in support of the first prediction. These results are consistent with the hypothesis proposed in two previous studies (14, 17) that gastric distension, rather than nutrient content, is likely to be the major determinant of the enhanced food intake-reducing effect of CCK when it is combined with a large preload. These results are also consistent with earlier studies in monkeys (15) that showed that a low dose of CCK was able to reduce food intake only when combined with a saline gastric preload as well as with a more recent study that showed that CCK-A receptors mediated the effect of banana drink preload that did not itself elevate plasma CCK levels (6).

The second prediction concerned intakes with CCK and distension separately. Intake reductions with CCK alone and distension alone were similar in men and women, with a single notable exception: women reduced intake significantly when they were given CCK without distension (by 121 g), whereas men did not. Consequently, distension did not further decrease intake under CCK infusion in women, whereas it did in men. These sex differences in the pattern of response to CCK and distension may be either attributable to inadequate statistical power or the result of an effectively larger dose in women than men, because the women were slightly smaller and lighter. Nevertheless, they deserve further study, since they could contribute to the frequently found difference in the intakes of men and women.

The combined effect of CCK and distension could also be interpreted as an enhancement of distension’s effect on sensitizing whatever mechanisms reduce food intake in response to CCK. We favor the hypothesis that CCK enhances the distension effect, rather than distension enhancing the CCK effect, mainly because recording from the afferent vagus has shown that mechanoreceptors, which are sensitive to gastric stretch, respond more strongly in the presence of CCK (19). However, it is also possible for cells that respond to CCK, in the absence of distension, to respond more strongly when the stomach was distended.

To interpret the small but significant feeling of sick reported by the subjects, we undertook other studies in which subjects were asked to make ratings of their feelings in situations recalled from the past. When those ratings were compared with the ratings in the present study, it was clear that the small increase seen in the present studies was not consistent with either a normal dinner (which produced an almost 0 level of sick), a meal that disagreed strongly when the stomach was distended.

Palatability. No differences were found in yogurt shake liking ratings (palatability) after the lunch meal among any of the conditions. The grand mean ± SD of all ratings (on a scale of 1–9) was 6.9 ± 0.6 (39 df for within-subjects root MSE (same as SD), root MSE between was 1.8 (13 df)). As expected, there were significant differences in liking ratings among subjects ($F_{13,39} = 8.11, P < 0.0001$).

**DISCUSSION**

The main results for the genders together showed a significant reduction in intake after a combination of CCK and distension, in support of the first prediction. These results are consistent with the hypothesis proposed in two previous studies (14, 17) that gastric distension, rather than nutrient content, is likely to be the major determinant of the enhanced food intake-reducing effect of CCK when it is combined with a large preload. These results are also consistent with earlier studies in monkeys (15) that showed that a low dose of CCK was able to reduce food intake only when combined with a saline gastric preload as well as with a more recent study that showed that CCK-A receptors mediated the effect of banana drink preload that did not itself elevate plasma CCK levels (6).

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To interpret the small but significant feeling of sick reported by the subjects, we undertook other studies in which subjects were asked to make ratings of their feelings in situations recalled from the past. When those ratings were compared with the ratings in the present study, it was clear that the small increase seen in the present studies was not consistent with either a normal dinner (which produced an almost 0 level of sick), a meal that “disagreed” with the subject (which produced levels of sick of 100 mm (out of 150 mm)), or the largest meal ever eaten (which produced a rating of 77 mm). Thus the combination of balloon filling and CCK infusion produced a sensation that was different from both normal meal fullness and full-blown discomfort induced by an excessive or disagreeable meal. These results suggest that the combination of a gastric distension with stimulation of CCK receptors could lead to the development of an effective appetite-suppressing agent that relies on natural satiety-inducing processes.

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REFERENCES


