anhydrous sodium sulfate. The amine was converted in the usual manner to the hydrochloride and recrystallized.

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Cholecystokinin-Like Activities in Guinea Pigs and in Dogs of the C-Terminal Octapeptide (SQ 19,844) of Cholecystokinin

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Abstract □ The synthetic C-terminal octapeptide of cholecystokinin (CCK), SQ 19,844, caused CCK-like contractile activities of excised gallbladder and ileal strips of guinea pigs, of gallbladder preparations *in situ* in anesthetized guinea pigs, and of gallbladder and duodenal preparations *in situ* in anesthetized dogs. In these preparations, SQ 19,844 was about 10 and 2.5 times more potent than CCK on a weight basis and molar basis, respectively. The duration of the effect of SQ 19,844 on the gallbladder was about one-half that of CCK. In fasted unanesthetized dogs with gastric pouches, the secretory stimulant potency of SQ 19,844 was only about four-fifths and one-third that of CCK on a weight basis, and molar basis, respectively. The C-terminal tetrapeptide, which was more potent than either SQ 19,844 or CCK as a gastric secretory stimulant, was considerably less potent in contracting the gallbladder.

Keyphrases □ Cholecystokinin—gallbladder-intestinal contraction, gastric secretion □ C-terminal octapeptide—gallbladder-intestinal contraction, gastric secretion □ Gallbladder contraction—C-terminal tetrapeptide, protected □ C-terminal tetrapeptide, protected—gastric secretion □ Peptides, cholecystokinin related—gallbladder-intestinal contraction, gastric secretion

In 1928, Ivy and Oldberg reported (1) that an extract of the upper intestinal mucosa promoted contraction and evacuation of the gallbladder. This extract contained a substance that they named cholecystokinin, herein designated as CCK. CCK is a single-chain polypeptide with 33 aminoacid residues (2). The C-terminal pentapeptide of CCK is identical (3) with that of gastrin (4, 5). Harper and Raper in 1943 (6) and Crick *et al.* in 1949 (7) demonstrated that the mucosa of the upper intestine contained a substance that promoted pancreatic secretion of enzymes; they named this substance pancreozymin. Mutt and Jorpes (8, 9) have found that CCK activity and pancreozymin activity accompanied each other during purification; accordingly, CCK and pancreozymin may be identical (8–10). Mutt and Jorpes (8–10) reported that pure CCK, tested on the guinea pig gallbladder, assays at 3,000 Ivy dog units/mg.

A partial determination of the aminoacid sequence of CCK was reported recently by Mutt and Jorpes (10–12), who also isolated the C-terminal octapeptide of CCK after tryptic digestion (9–12) and noted that it was very active in contracting the gallbladder and in promoting secretion of pancreatic enzymes. This octapeptide was synthesized by Ondetti *et al.* (13) at the Squibb Institute and is referred to as SQ 19,844. The sequence of aminoacid residues in CCK and in SQ 19,844 is as follows:

$$\text{Lys}\cdot(\text{Ala}_1, \text{Gly}_1, \text{Pro}_1, \text{Ser}_1)\cdot\text{Arg}\cdot\text{Val}\cdot(\text{Ileu}_1, \text{Met}_1, \text{Ser}_1)\cdot\text{Lys}\cdot$$
$$\text{Asn}\cdot(\text{Asx}_1, \text{Glx}_1, \text{His}_1, \text{Leu}_2, \text{Pro}_1, \text{Ser}_2)\cdot\text{Arg}\cdot\text{Ileu}\cdot(\text{Asp}_1, \text{Ser}_1)\cdot$$
$$\text{Arg}\cdot\text{Asp}\cdot\underset{\displaystyle\text{SO}_3\text{H}}{\text{Tyr}}\cdot\text{Met}\cdot\text{Gly}\cdot\text{Trp}\cdot\text{Met}\cdot\text{Asp}\cdot\text{Phe}\cdot\text{NH}_2$$

Cholecystokinin (CCK)

$$\underset{\displaystyle\text{SO}_3\text{H}}{\text{Asp}}\cdot\text{Tyr}\cdot\text{Met}\cdot\text{Gly}\cdot\text{Trp}\cdot\text{Met}\cdot\text{Asp}\cdot\text{Phe}\cdot\text{NH}_2$$

SQ 19,844

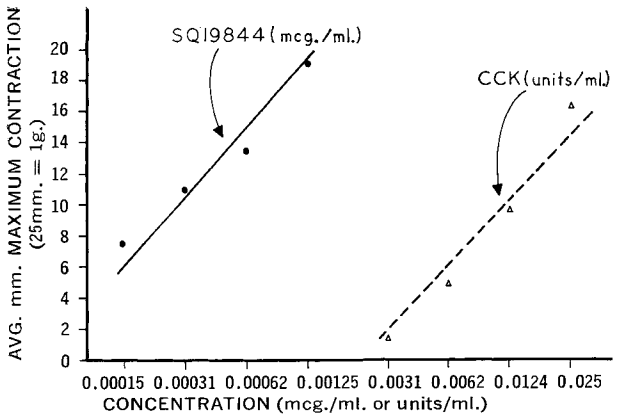

Figure 1—*Peak contractile response curves* in vitro *of SQ 19,844 and CCK on gallbladder strips of guinea pigs. Concentrations are shown on log-scale.*

The CCK-like activity of SQ 19,844 has been compared with that of one preparation of CCK obtained from Vitrum A/B of Sweden. In some instances, the C-terminal tetrapeptide[1] with a benzyloxycarbonyl protecting group on the tryptophan component was also tested.

This report describes several effects of these peptides on gallbladder contractility, intestinal motility, gastric secretion, and systemic blood pressure of either guinea pigs or dogs.

METHODS

In Vitro Preparations—Gallbladder strips (14) from either male or female guinea pigs (weight, 150–200 g.) were mounted in 10-ml. tissue baths containing Krebs solution at 36.5° and bubbled with 95% O_2–5% CO_2. One strip was taken from each animal. Isometric responses of the strips, initially under 0.5-g. tension, were recorded *via* force-transducers (Grass FT.03) connected to a dynograph (Beckman). Treatment time was 3 min. for each peptide.

In other tests, contractile effects on guinea pig ileal segments were studied similarly, except that the initial tension imposed was 2 g. and treatment time was 2 min.

The peptides employed both *in vitro* and *in vivo* were SQ 19,844 dissolved in 0.5 *N* $NaHCO_3$, CCK (Vitrum No. 211017) dissolved in physiological saline, and protected C-terminal tetrapeptide dissolved in 10% *N,N*-dimethylacetamide in saline. The vehicles alone caused little or no effect in any of the tests. The peptides were added in random order to each tissue bath, each in a volume of 0.05 ml. Four washings totaling 25 ml. of peptide-free Krebs solution were used after each treatment. The period between additions of peptide ranged from 5–15 min., depending on the time needed for relaxation of the tissue. Four by four (8-point) factorially designed assays were conducted on each gallbladder strip. Biometrical evaluation[2] was performed according to the methods of Bliss (15). The peak contractile response was the dependent variable. The bath concentrations ranged from 0.15–1.25 ng./ml. for SQ 19,844, from 0.0031–0.025 Ivy dog units/ml. for CCK, and from 0.005–0.5 mcg./ml. for protected C-terminal tetrapeptide.

In the case of the ileal contractions induced by the peptides, only graphical estimates of approximate potency were made. The bath concentrations ranged from 0.20–12.8 ng./ml. for SQ 19,844, and from 0.0062–0.40 Ivy dog units/ml. for CCK.

In Situ Preparations of Anesthetized Guinea Pigs—Male guinea pigs each weighing from 500–700 g. were fasted overnight and anesthetized with urethane, 2 g./kg. s.c. The gallbladder was exposed after a midline abdominal incision. A silk line was attached to the outer wall of the fundus of the gallbladder (16) and connected to a force-transducer (Grass FT.03) coupled to a dynograph (Beckman). An initial tension of 2 g. was imposed prior to monitoring isometric contractions. In some of the guinea pigs, systemic blood pressure was recorded from a carotid artery *via* a pressure transducer (Statham) coupled to the dynograph. Each randomized dose of peptide, given in 0.1 ml. of solution was washed into a jugular vein with 0.5 ml. of physiological saline within a period of 10–20 sec. At least 10 min. elapsed between injections. Factorially designed 8-point assays of gallbladder contractile activity were conducted and biometrically evaluated (15); the peak contractile effect on the gallbladder was the dependent variable. The i.v. dose ranges were 0.97–7.8 ng./kg. for SQ 19,844 and 0.0635–0.50 Ivy dog units for CCK.

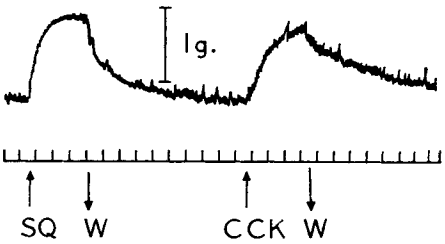

Figure 2—*Example of* in vitro *contractile effects of SQ 19,844 (SQ), 1.25 ng./ml., and of CCK, 0.025 Ivy dog unit/ml., on a guinea pig gallbladder strip. W = wash. Time marks at 1-min. intervals.*

In Situ Preparations of Anesthetized Dogs—Mongrel dogs of either sex, ranging in weight from 10–13.5 kg., were fasted overnight and anesthetized with urethane, 1.8–2.2 g./kg., i.v. A femoral vein and the contralateral femoral artery were cannulated for injections and blood pressure monitoring, respectively. Blood pressure was recorded *via* a pressure transducer (Statham) connected to a dynograph (Beckman). The gallbladder and duodenum were exposed after a midline abdominal incision. The dome of the gallbladder was cannulated with a flanged polyethylene tube and the cystic duct was ligated or clamped, according to the method of Ivy and Janecek (17). The intragallbladder pressure was monitored continuously with a saline-filled pressure transducer (Statham) coupled to the dynograph. If pressure in the gallbladder immediately after cannulation was less than 5–10 cm. of water, enough saline was added to the system to reach this pressure range.

A 4-cm. longitudinal incision was made in the duodenum, starting approximately 2.5 cm. from the pylorus. A small latex balloon (approximately 2 cm. in diameter × 6 cm. in length), attached to a pressure transducer (Statham), was passed caudad for about 20 cm. through the opening in the duodenum. Pressure in the balloon, connecting tubing, and transducer, all filled with water, was adjusted to at least 5–10 cm. of water at the beginning of each test. Injections of peptides (1 ml. of solution) were made i.v. at 15-min. intervals or longer and washed in with 1 ml. of saline; each injection was made within 10–20 sec. The interval between injections depended on the time required for the intragallbladder pressure, systemic blood pressure, or duodenal-balloon pressure to return to or near predose levels.

The i.v. doses employed in the dog ranged from 8–64 ng./kg. for SQ 19,844 and from 0.125–1.0 Ivy dog units/kg. for CCK. A total of 12 or 18 injections was made into each dog. Graphical estimates of approximate relative potency were determined for the peak contractile effects on the gallbladder and duodenum.

In Vivo Preparations of Unanesthetized Dogs—Repeated determinations of the gastric secretory responses after single subcutaneous doses (0.10 or 0.20 ml./kg.) of these peptides were determined in one dog with a Heidenhain pouch and in one dog with a Pavlov pouch, each weighing about 11 kg. These dogs were fasted about 18 hr. before each test, but were allowed water *ad libitum*. On the day of test, at least two control collections of pouch secretions were made at intervals of 0.5 hr. After each s.c. dose, collections were made at 0.5-hr. intervals for as long as 5 hr. The volume (*V*), pH (glass electrode Beckman Zeromatic meter), titratable acidity to pH 7 (*TA*), and titratable acidity output (*TAO*, calculated as $TA \times V$) were determined on any collection of 0.5 ml. or more. *V*, *TA*, and *TAO* were expressed as ml., meq./l., and μeq., respectively. The effective s.c. doses employed ranged from 1.0–4.0 mcg./kg. for SQ 19,844, from 8–32 Ivy dog units/kg. for CCK, and

[1] Tetragastrin, prepared by Dr. M. Ondetti and associates at the Squibb Institute for Medical Research, New Brunswick, N. J.

[2] Kindly conducted by Mr. A. M. Combs and Dr. R. S. Valand of Scientific Systems, Squibb Beech-Nut, Inc.

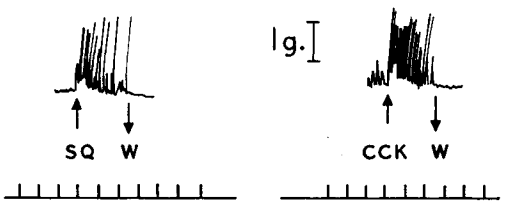

Figure 3—*Example of* in vitro *contractile effects of SQ 19,844 (SQ), 12.8 ng./ml., and of CCK, 0.40 Ivy dog unit/ml., on the same guinea pig ileal segment. W = wash. Time marks at 1-min. intervals.*

from 0.4–10 mcg./kg. for protected C-terminal tetrapeptide. Neither dog was tested with peptide at intervals of less than 2 days.

RESULTS

In Vitro Preparations—With reference to peak contractile effects on the gallbladder strips, 1 mg. of SQ 19,844 was equivalent to 26,010 Ivy dog units of CCK, with a potency range of 19,574–34,562 units at the 95% confidence level (Fig. 1). The dose-response curves did not depart from parallelism or linearity at $p = 0.05$. A representative tracing is shown in Fig. 2.

The contractile effect of SQ 19,844 on the gallbladder strips appeared to develop more rapidly than did that of CCK; also the reversibility or relaxation of the strips after washing with Krebs solution occurred more rapidly in the case of the octapeptide. The average times for the development of peak contractile effects ranged from 1.6–2.0 min. for SQ 19,844 and from 2.0–2.8 min. for CCK. The average times for 50% relaxation after washing ranged from 0.25–1.1 min. for SQ 19,844 and from 0.35–1.9 min. for CCK. The average times for complete relaxation after washing ranged from 0.70–3.5 min. for SQ 19,844 and from 1.1–5.4 min. for CCK.

As a contractile agent for gallbladder strips, protected C-terminal tetrapeptide was only about 1/1000 to 1/100 times as potent as SQ 19,844.

Graphical estimates of contractile activity on excised ileal strips of guinea pigs indicated that 1 mg. of SQ 19,844 was equivalent to about 30,000 Ivy dog units of CCK. Unlike the contractile responses of the guinea pig gallbladder strips, the rates of development, as well as the reversibility, of the contractile responses of ileal strips to SQ 19,844 were similar to those of CCK. The contractile effects of both SQ 19,844 and CCK were promptly reversed after washing the ileal strips (Fig. 3).

In Situ Preparations of Anesthetized Guinea Pigs—In urethanized guinea pigs, 1 mg. of SQ 19,844 was equivalent to 30,304 Ivy dog units of CCK, with a potency range of 23,872–38,469 units at the 95% confidence level (Fig. 4). A representative tracing is shown in Fig. 5.

The reversibility of the contractile effects of SQ 19,844 on guinea pig gallbladder *in situ* was more rapid than that shown by this

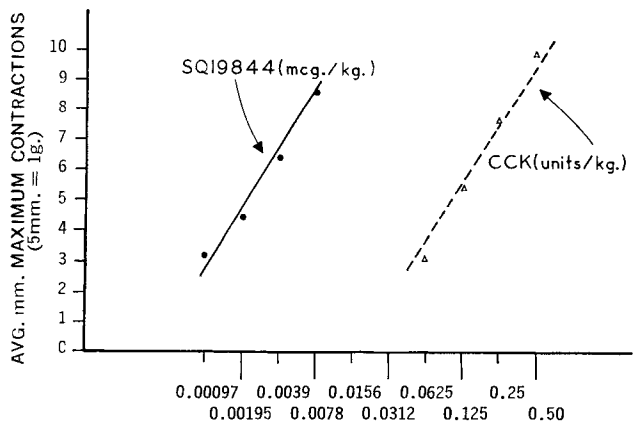

Figure 4—*Peak contractile response curves of SQ 19,844 and CCK* in situ *on gallbladders of five urethanized guinea pigs. Doses are shown on log-scale.*

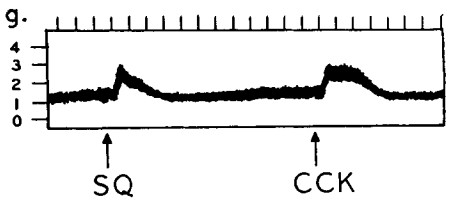

Figure 5—*Example of* in situ *contractile effects of SQ 19,844 (SQ), 7.8 ng./kg., and of CCK, 0.25 Ivy dog unit/kg., on guinea pig gallbladder. Time marks at 1-min. intervals.*

sample of CCK. Although the average times required to reach peak contractile effects were similar for both peptides, each ranging from 1.0–1.2 min., the average times for 50% decrease from peak tension ranged from 0.8–1.1 min. for SQ 19,844 and from 1.4–2.3 min. for CCK. Complete recovery times averaged 1.6–2.6 min. for SQ 19,844 and 2.7–5.3 min. for CCK.

Protected C-terminal tetrapeptide was inactive on guinea pig gallbladder at i.v. doses up to 2 mcg./kg.; it was estimated to be less than 1/2000 as potent as SQ 19,844 i.v.

In three guinea pigs in which systemic blood pressure was also monitored, dosage with either SQ 19,844 or CCK produced little or no gross change in blood pressure. Only at the one or two highest doses was a minimal, transient hypotension noted; this was at most a decrease of 5 mm. of Hg in blood pressure, lasting about 2 min. for SQ 19,844 and about 3–5 min. for CCK from the time of injection.

In Situ Preparations of Anesthetized Dogs—Graphical analyses of data from urethanized dogs indicated that 1 mg. of SQ 19,844 i.v. was equivalent to approximately 20,000 Ivy dog units of CCK, with reference to both maximum increases in intragallbladder pressures and peak duodenal contractile effects (Fig. 6).

SQ 19,844 i.v. not only produced its peak contractile effect on dog gallbladder about 1.5 times faster than did this sample of CCK, but this effect of SQ 19,844 wore off about 2 to 3 times more rapidly. The average times required to attain peak increases in intragallbladder pressure ranged from 1.2–1.5 min. for SQ 19,844 and from 2.1–2.5 min. for CCK. The average times needed for 50% recovery ranged from 1.4–3.5 min. for SQ 19,844 and from 4.6–9.4 min. for CCK. Complete recovery times averaged 4.3–10.6 min. for SQ 19,844 and 10.6–23.6 min. for CCK.

SQ 19,844 i.v. produced its peak contractile effect on dog duodenum about one to two times faster than did CCK; this effect of the octapeptide wore off about two times faster than did that of CCK. The average times required to attain peak contractile effects on the duodenum ranged from 0.25–0.76 min. for SQ 19,844 and from 0.45–0.69 min. for CCK. These contractions subsided rap-

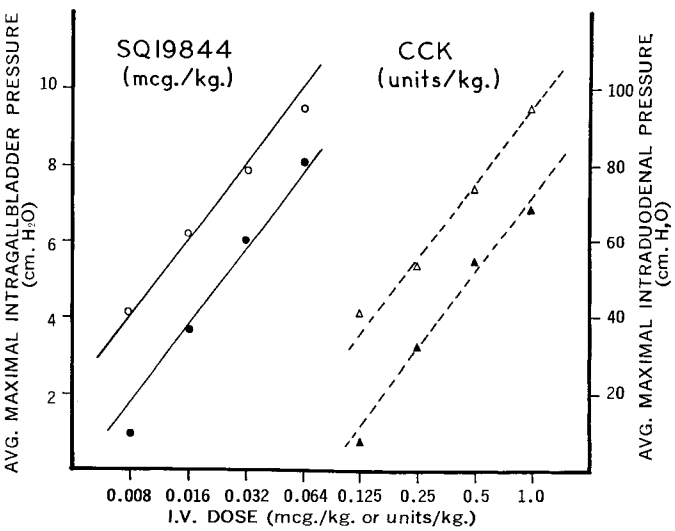

Figure 6—*Peak contractile response curves of SQ 19,844 and CCK* in situ *in four urethanized dogs. Key: ○ and △, intraduodenal pressure; ● and ▲, intragallbladder pressure. Doses are shown on log-scale.*

Table I—Mean Gastric Secretory Responses in Fasted Unanesthetized Dogs after s.c. Dosage with Peptides

Peptide	Dose/kg.	Pavlov Pouch No. 3219 Vol.[a] ml.	Acidity[a,b] μeq.	Approx. Duration hr.	N[c]	Heidenhain Pouch No. PB 383 Vol.,[a] ml.	Acidity[a,b] μeq.	Approx. Duration hr.	N[c]
Vehicle control[d]	0.10 ml.	4.2	85	0.5	2	2.3	45	0.5	2
CCK	8.0 IDU[e]	1.4	28	0.5	2	2.8	105	1.0	2
	16.0 IDU	10.7	895	2.0	2	2.7	155	1.3	2
	32.0 IDU	14.8	1522	3.0	3	7.3	528	2.0	2
SQ 19,844	1.0 mcg.	4.3	190	1.5	2	2.9	160	1.3	2
	4.0 mcg.	11.3	915	2.3	2	5.5	370	1.0	2
Protected C-terminal tetrapeptide	0.4 mcg.	8.2	510	2.0	2	2.1	53	1.3	2
	2.0 mcg.	18.5	2000	2.5	3	7.0	485	1.3	2
	10.0 mcg.	65.9	8809	5.0	3		not tested		

[a] Cumulative totals. [b] Titratable acidity to pH 7. [c] Number of tests. [d] 0.5 *N* $NaHCO_3$ [e] Ivy dog units.

idly; the average times for complete recovery ranged from 1.0–2.5 min. for SQ 19,844 and from 2.2–4.3 min. for CCK.

Thus, the contractile effects of either SQ 19,844 or CCK on the duodenum occurred about two to three times more rapidly than did those on the gallbladder. Furthermore, the duration of their contractile effects on the duodenum was only about one-fifth that of their effects on the gallbladder.

Slight and transient hypotensive effects occurred in the anesthetized dogs after the three highest doses of either peptide. Decreases in blood pressure of 5–20 mm. of Hg, lasting 1–5 min., occurred after injections of the octapeptide; similar decreases, lasting about 3–15 min., occurred after injections of CCK.

A representative set of tracings of the recorded responses in one of the anesthetized dogs is shown in Fig. 7.

In Vivo Preparations of Unanesthetized Dogs—The results of s.c. administration of these peptides to fasted dogs with a Heidenhain or Pavlov pouch are summarized in Table I. These results indicate that 4 mcg. of SQ 19,844 were roughly equivalent to 16 Ivy dog units of CCK and to 0.40-2 mcg. of protected C-terminal tetrapeptide in stimulating pouch secretions in terms of total volumes, total titratable acidities, and durations of augmented secretory activity. In these tests, 1 mg. of SQ 19,844 s.c. was approximately equivalent to 4,000 Ivy dog units of CCK. Furthermore, SQ 19,844 s.c. was about one-tenth to one-half as potent as protected C-terminal tetrapeptide. No gross differences in the durations of roughly equivalent secretory effects were apparent, however, among these three peptides.

Rapid intravenous injections of SQ 19,844 were made at 15-min. intervals into a normotensive, unanesthetized male beagle (wt. 8.1 kg.) with indwelling cephalic venous and carotid arterial cannulae.[3] Each injection, consisting of 1 ml. of peptide solution followed by 0.5 ml. saline, was completed within 20 sec. Blood pressure and heart rate were monitored on a dynograph (Beckman) *via* a pressure transducer (Statham) and a cardiotachometer (Beckman).

Eight and 16 ng./kg. of SQ 19,844 had little or no effect on blood pressure or heart rate, but 32, 64, 128, 256, and 512 ng./kg. produced transient hypotensive effects. These effects, which consisted of decreases of 16–36 mm. Hg in mean blood pressure, occurred only during the first 1–2 min.; recovery to predose levels of blood pressure occurred within the next 2–3 min. At doses of 64–512 ng./kg., SQ 19,844 also produced transient bradycrotic effects of similar duration; these effects consisted of decreases in heart rate of 10–46 beats/min.

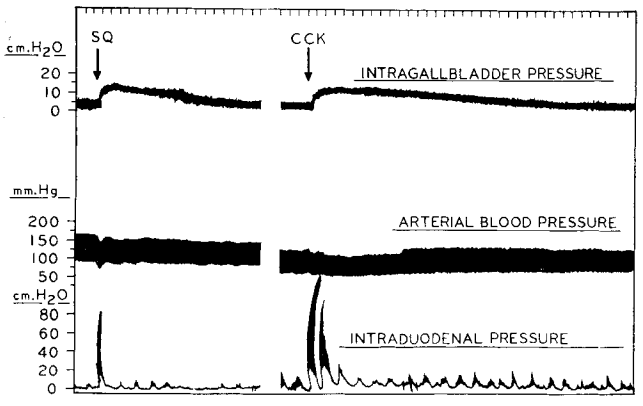

Figure 7—*Example of effects of i.v. SQ 19,844 (SQ), 64 ng./kg., and CCK, 1.0 Ivy dog unit/kg., on intragallbladder pressure, femoral arterial blood pressure, and intraduodenal pressure in the same urethanized dog. Time marks at 1-min. intervals.*

DISCUSSION AND CONCLUSIONS

The synthetic C-terminal octapeptide of CCK, *i.e.*, SQ 19,844, caused cholecystokinin-like contractile activities of the gallbladder and small intestine of the guinea pig and dog. The log dose-peak response curves of SQ 19,844 and of CCK were parallel to each other; therefore, the mechanisms of action of SQ 19,844 on these tissues or organs presumably are not dissimilar to those of CCK.

The contractile activities of SQ 19,844 relative to those of CCK were similar on the gallbladder and small intestine of the guinea pig and dog; in the tests carried out both *in vitro* and *in vivo*, 1 mg. of SQ 19,844 was equivalent to about 20,000–30,000 Ivy dog units of CCK. Pure CCK (mol. wt. 3,950) represents 3,000 Ivy dog units/mg. (8–10). The C-terminal octapeptide SQ 19,844 (mol. wt. 1,142) was, on a weight basis and molar basis, about 10 times and 2.5 times, respectively, more potent than CCK.

The durations of the contractile effects of SQ 19,844, however, were about one-half those of the sample of Vitrum CCK used in these tests. Speculatively, the results obtained both *in vitro* and *in vivo* suggest that the shorter duration of action of SQ 19,844 on the gallbladder may be related to (*a*) more rapid binding at the contractile receptor sites; (*b*) more rapid release or diffusion from such sites; or (*c*) more rapid enzymatic degradation of the octapeptide by peptidases to less active or inactive fragments. Furthermore, the time needed for enzymatic degradation of the 33 aminoacid peptide CCK to smaller active peptides, one of which could possibly be the C-terminal octapeptide, could account, at least in part, for the longer duration of action of CCK. A different sample of CCK[4] manifested a duration of action similar to that of the Vitrum sample of CCK, based on comparative tests on excised strips of guinea pig gallbladder and also on the gallblader *in situ* of the anesthetized guinea pig given the polypeptide i.v.

Protected C-terminal tetrapeptide (mol. wt. 730), on both a weight basis and molar basis, was from 1/1000 to 1/100 as potent as SQ 19,844 in contracting the excised gallbladder strip of the guinea pig. Given i.v., this tetrapeptide was even less active on the guinea pig gallbladder *in situ;* it was less than 1/2,000 as potent as SQ 19,844 on both a weight basis and molar basis. Protected C-terminal tetrapeptide *in vitro* was from 1/100 to 1/10 and from

[3] This test was conducted by Dr. G. L. Hassert and Mr. A. Peterson of the Squibb Institute for Medical Research, New Brunswick, N. J.

[4] Kindly supplied by Dr. V. Mutt, Karolinska Institute, Stockholm, Sweden (lot No. 26811).

1/500 to 1/50 as potent as CCK on a weight basis and molar basis, respectively; given i.v., this tetrapeptide was less than 1/200 and less than 1/1000 as potent as CCK on a weight and molar basis, respectively, in contracting the gallbladder of the guinea pig.

Vagne and Grossman (18) reported that C-terminal tetrapeptide trifluoroacetate, given i.v. to the unanesthetized dog, was 1/24 as potent as CCK on a weight basis and 1/143 as potent on a molar basis, with reference to contractile activity on the gallbladder. Results from this laboratory *in vitro*, but not *in situ*, with guinea pig gallbladder are in general agreement with those of Vagne and Grossman. Each of at least three factors could contribute to the difference in activity noted *in vivo;* namely, difference in the form of tetrapeptide used, the presence or absence of anesthesia, and the difference in animal species.

CCK-pancreozymin has been reported to inhibit gastric secretion in the unanesthetized dog with a gastric pouch or fistula when the background secretion has been kept at a high level by a prior test meal, or by s.c. or continuous i.v. dosage with gastrin or gastrin-like peptide, histamine, or cholinergic agents (19–21). When the background secretory level is low, as in fasted dogs, however, CCK stimulated gastric secretions (22). The present authors' results in fasted dogs with a Heidenhain or Pavlov pouch, which received relatively high s.c. doses of CCK or of SQ 19,844, are in general agreement with the latter finding. One milligram of SQ 19,844 s.c. was equivalent to about 4,000 Ivy dog units of CCK in augmenting gastric secretions; thus, SQ 19,844, on a weight basis and molar basis, respectively, was about four-fifths and one-third as potent as CCK.

In these same fasted, unanesthetized dogs with gastric pouches, protected C-terminal tetrapeptide s.c., on a weight basis, was from 2 to 10 times more potent than SQ 19,844 in augmenting gastric secretions. On a molar basis, the protected tetrapeptide was from 1 to 6 times more potent than SQ 19,844. Relative to CCK, protected C-terminal tetrapeptide on a weight basis, was from 2.5 to 13 times as potent; on a molar basis, protected C-terminal tetrapeptide was from 0.4 to 2 times as potent.

No gross differences in the durations of the secretory effects of either SQ 19,844, CCK, or protected C-terminal tetrapeptide were apparent in these fasted, unanesthetized dogs with gastric pouches. The similar durations of secretory effects of SQ 19,844 and of protected C-terminal tetrapeptide and their similar molar potencies relative to CCK (range 0.3–2) may be associated with the presence of a common unit, the C-terminal tetrapeptide. This is in sharp contrast to the wider range of their molar potencies relative to CCK (range 0.002–2.5) as contractile agents on the gallbladder. This possibly indicates that several more specific aminoacids need be added to the N-terminal end of this tetrapeptide in order to increase CCK-like activity on the gallbladder (18). Others have reported (23), for example, that the C-terminal heptapeptide of CCK, like the octapeptide SQ 19,844, is highly potent as a contractile agent on the gallbladder.

Other actions of SQ 19,844 remain to be assessed. These include effects on (*a*) pancreatic exocrine secretion; (*b*) gastric secretion in animals with a high level of background gastric secretion; and (*c*) motility and tone of different segments of the gastrointestinal tract. Further studies on the cardiovascular system also remain to be conducted. Thus far, the results indicate that, in the dog, only slight and very transient hypotensive effects are produced by SQ 19,844 after i.v. doses that are from 2 to 64 times greater than the doses effective on the gallbladder.

A reassessment of all these qualitative and quantitative relationships of the C-terminal octapeptide SQ 19,844, relative to CCK, may be needed when pure natural or synthetic cholecystokinin becomes available. Meanwhile, the C-terminal octapeptide or related peptides may prove to be useful pharmacological, diagnostic, or therapeutic agents affecting the biliary, intestinal, and pancreatic functions.

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