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The effects of a peripherally acting cholecystokinin$_1$ receptor antagonist on food intake in rats: implications for the cholecystokinin-satiety hypothesis

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Abstract

The observation that systemic administration of the peptide cholecystokinin (CCK) inhibits food intake in mammalian species has led to the hypothesis that endogenous peripheral CCK released from the small intestine during a meal acts as a satiety factor. It was predicted that if CCK does play an important role in satiety, then systemic administration of a specific CCK receptor antagonist should block the effects of the endogenous peptide released during a meal and increase food intake. The present study was undertaken to test the hypothesis by investigating the effects of the cholecystokinin$_1$ (CCK_1) receptor antagonist *N*-alpha-3′-quinolinoyl-D-Glu-*N*,*N*-dipentylamide dicyclohexylammonium (A70104), which is unlikely to cross the blood–brain barrier, on food intake in rats. A70104 (20–200 μg/kg, i.p.) had no any significant effect on the intake of a test meal in rats under different experimental conditions. However, pretreatment of rats with A70104 (50 μg/kg, i.p.) abolished the inhibitory effects of exogenous peripheral CCK (5 μg/kg, i.p.) on food intake. The findings that A70104 had no effect on food intake when administered on its own, but abolishes the suppressant effect of exogenous peripheral CCK, suggest that endogenously released peripheral CCK does not play an important role as a satiety factor in rats.

Keywords: Cholecystokinin; CCK_1 receptor antagonist; A70104; Devazepide; Satiety; Food intake

1. Introduction

Gibbs et al. (1973) demonstrated that intraperitoneal (i.p.) administration of the sulphated cholecystokinin octapeptide (CCK) reduces food intake in hungry rats by an apparently non-aversive mechanism, and proposed that endogenous CCK released from the small intestine during a meal acts in a negative feedback manner to induce a state of post-prandial satiety. Subsequent studies have confirmed that systemic administration of CCK inhibits food intake in a number of other species, including pig, chicken, dog, mouse, monkey and man (Falasco et al., 1979; Savory and Gentle, 1980; Anika et al., 1981; Kissileff et al., 1981; Bado et al., 1988; Inui et al., 1988; Silver et al., 1989; Ebenezer et al., 1990). As the peptide cannot penetrate the blood–brain barrier (Passaro et al., 1982), it is likely that systemically administered CCK acts at a peripheral site to inhibit feeding (Weller et al., 1990). Results from a number of studies have suggested that peripheral exogenous CCK activates CCK receptors in the abdomen and that this information is relayed via vagal afferents to brain regions involved in the regulation of feeding to induce behaviour consistent with satiety (see Smith and Gibbs, 1992; Crawley and Corwin, 1994; Baldwin et al., 1998). Likewise, it has also been mooted that if endogenous CCK released from the small intestine during a meal acts as a satiety factor, then it must also act at a similar peripheral site to signal central nervous system (CNS) areas involved in feeding behaviour via vagal afferents (Smith and Gibbs, 1992, 1994).

In order to test the hypothesis that CCK is a peripherally acting satiety factor, it was argued that systemic administration of a specific CCK receptor antagonist should block the effects of the endogenous peptide released from the small intestine, and increase the amount of food eaten during a meal (Hewson et al., 1988; Ebenezer et al., 1990). In agreement with this prediction, it has been shown that the

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cholecystokinin$_1$ (CCK_1) receptor antagonist devazepide (formerly coded as L364,718 and MK329) (Chang and Lotti, 1986) increases meal size when administered systemically to several species including rat, pig, mouse, monkey, chicken and man (Hewson et al., 1988; Ebenezer et al., 1990; Wolkowitz et al., 1990; Weatherford et al., 1992; Moran et al., 1993; Covasa and Forbes, 1994). Moreover, devazepide also blocks the hypophagia produced by systemically administered CCK, and these findings suggest that the inhibitory action of the peptide on feeding is mediated by peripheral CCK_1 receptors (Hewson et al., 1988; Weller et al., 1990; Ebenezer et al., 1990). On the basis of the results obtained mainly with devazepide, some workers have concluded that the hypothesis that endogenous peripheral CCK is an important satiety factor is proven (Smith and Gibbs, 1992, 1994).

More recently, it has been demonstrated that intracerebroventricular (i.c.v.) administration of devazepide to pigs (Baldwin and de la Riva, 1992) and rats (Ebenezer, in press) increases food intake at doses that are too low to be effective peripherally, indicating a central site of action. As devazepide readily crosses the blood–brain barrier to enter the brain (Pullen and Hodgson, 1987), it is conceivable that systemic administration of the CCK_1 receptor antagonist increases food intake by a central mode of action rather than by blocking the effects of endogenous peripheral CCK (see Baldwin et al., 1998). It was reasoned that if it could be demonstrated that a specific CCK_1 receptor antagonist that does not cross the blood–brain barrier increases food intake, then this would lend support to the hypothesis that peripheral CCK is involved in satiety (Ebenezer and Parrott, 1993). On the other hand, if such a drug does not increase food intake, then it is unlikely that endogenous peripheral CCK acts as a satiety factor. The availability of CCK_1 receptor antagonists, such as 2-naphthalenesulphanyl-L-aspartyl-2-(phenethyl)amide (2-NAP) (Hull et al., 1993) and *N*-alpha-3′-quinolinoyl-D-Glu-*N*,*N*-dipentylamide dicyclohexylammonium (A70104; Asin et al., 1992a,b), that do not readily penetrate the blood–brain barrier (Asin et al., 1992b; Ebenezer and Parrott, 1993; Ebenezer and Baldwin, 1995) have provided an opportunity to test the CCK-satiety hypothesis more rigorously.

Results obtained in pigs have shown that both A70104 (Ebenezer and Parrott, 1993) and 2-NAP (Baldwin et al., 1994), administered intravenously (i.v.) over a wide range of doses, did not increase meal size in pigs deprived of food for 4 h. These workers used a similar experimental protocol employed previously, in which it was shown that devazepide given intravenously to pigs increases food intake by up to 50% (Ebenezer et al., 1990). They concluded that endogenous peripheral CCK does not play a role as a satiety factor in pigs.

Although the above studies suggest that endogenous peripheral CCK does not play an important role in mediating satiety in pigs, it is not possible to infer from these experiments that endogenous peripheral CCK does not play an important role in mediating satiety in other animals because specie differences exist in the functional responses to CCK (Ebenezer and Baldwin, 1991; Morley, 1987; Baldwin, 1992; Covasa and Forbes, 1994). However, Ebenezer and Baldwin (1995) found that intraperitoneal administration of 2-NAP did not increase meal size in rats, although pretreatment with 2-NAP blocked the hypophagic effect of intraperitoneally administered CCK. These results, therefore, suggest that endogenous peripheral CCK is also not important as a satiety factor in rats. The aim of the present study was to lend further support to this argument by investigating the effects of systemic administration of the CCK_1 receptor antagonist A70104 (Asin et al., 1992a,b; Ebenezer and Parrott, 1993) on food intake in rats. The ability of A70104 to antagonize the inhibitory effects of intraperitoneally administered CCK on food intake in rats was also examined.

2. Methods and materials

2.1. Experiment 1. Effects of A70104 on food intake in rats given an oral preload

Adult male Wistar rats ($n = 8$; body weight, 250–300 g) were housed in groups of four. They were deprived of food in their home cages for 20 h each day prior to training sessions or drug experiments, but had free access to water at all times. The animals were given four training sessions, separated by 2–3 days, during which time they were allowed free access to food in experimental cages measuring $32 \times 25 \times 19$ cm for 30 min (oral preload). The food was then removed and 30 min later they were allowed to feed for a further 120 min. The food was presented to the rats in shallow cylindrical cups, as described previously (Ebenezer, 1990). The nutrient composition of the food was as follows: protein 20%, oil 4.5%, carbohydrate 60%, fibre 5%, ash 7% plus traces of vitamins and metals. During experimental sessions that followed, the rats were injected intraperitoneally with either vehicle or A70104 (50 or 100 μg/kg) immediately after the oral preload. Thirty minutes later, the food was returned to the experimental cages, and the amount of food consumed by the rats during the subsequent 240-min test meal session was measured. A repeated measures design was used in which each rat received all treatments in a random fashion and 4–5 days separated the successive drug trials.

2.2. Experiment 2. Effects of A70104 and devazepide on food intake in 6-h-fasted rats

Male Wistar rats ($n = 8$; body weight, 230–295 g) were deprived of food in their home cages for 6 h prior to training sessions or drug experiments, but had free access to water at all times. They were given four training sessions, during which they were placed separately in experimental cages with access to food and water for 120 min. During experimental sessions, the animals were injected intraperitoneally

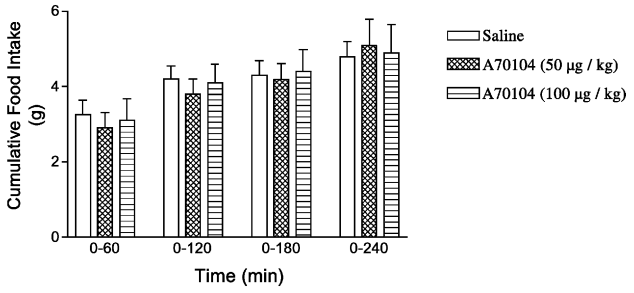

Fig. 1. Effects of A70104 on food intake in rats given an oral preload. The rats ($n=8$) were injected with vehicle or A70104 (50 or 100 μg/kg, i.p.) immediately after the oral preload, and 30 min prior to the 240-min test period. Vertical lines represent ± S.E.M.

with either vehicle or A70104 (20 or 100 μg/kg) and placed immediately in the experimental cages for 120 min. The amount of food consumed by the rats was measured. A repeated measures design was used in which each rat received all treatments in a random fashion and 4–5 days separated the successive drug trials.

A separate group of adult male Wistar rats ($n=8$; body weight, 235–330 g) were deprived of food in their home cages for 6 h each day prior to training sessions or drug experiments, but had free access to water at all times. A similar experimental procedure was used as described above, except that during experimental session, the rats were injected with either vehicle or devazepide (50 or 100 μg/kg) and placed immediately in the experimental cages for 120 min. The amount of food consumed by the rats was measured.

2.3. Experiment 3. Effect of A70104 pretreatment on CCK-induced hypophagia

Adult male Wistar rats ($n=8$; body weight, 260–300 g) were deprived of food in their home cages for 22 h each day, but had free access to water at all times. The animals were given four 2-h training sessions on separate days, during which time they were placed singly in experimental cages where they were allowed free access to food and water. During experimental sessions that followed, each rat was injected with either A70104 vehicle followed by saline, A70104 vehicle followed by CCK (5 μg/kg), A70104 (50 μg/kg) followed by saline or A70104 (50 μg/kg) followed by CCK (5 μg/kg). Both injections were given intraperitoneally. A period of 30 min separated the two injections. Immediately after the second injection, the rats were placed in the experimental cages, and the amount of food consumed by each animal was measured after 30 min. A repeated measures design was used, with each animal receiving all four treatments in random fashion.

2.4. Drugs used

A70104 (a gift from Abbott Laboratories, IL, USA) was dissolved in a vehicle containing methylsulfoxide (DMSO) and physiological saline solution (NaCl, 0.9% w/v) as described previously (Ebenezer and Parrott, 1993), to give an injection volume of 0.1 ml per 100 g body weight. The A70104 vehicle (Ebenezer and Parrott, 1993) was used in control experiments. Sulphated cholecystokinin octapeptide (Calbiochem-Novabiochem, Nottingham, UK) was dissolved in physiological saline solution to give an injection volume of 0.1 ml per 100 g body weight. Physiological saline was used as the control for CCK.

2.5. Statistics

The results from these experiments were analysed by analysis of variance (ANOVA) for repeated measures, and post hoc comparisons were carried out using the Tukey test.

3. Results

3.1. Experiment 1. Effects of A70104 on food intake in rats given an oral preload

A70104 (50 or 100 μg/kg, i.p.), administered immediately after the oral preload, did not significantly alter food consumption of the rats at any of the measurement time intervals during the 240-min test period (Fig. 1). The amount of food eaten during the oral preload (data not shown) was relatively constant from trial to trial (mean intake ± S.E.M. = 3.9 ± 0.6 g), and there were no significant

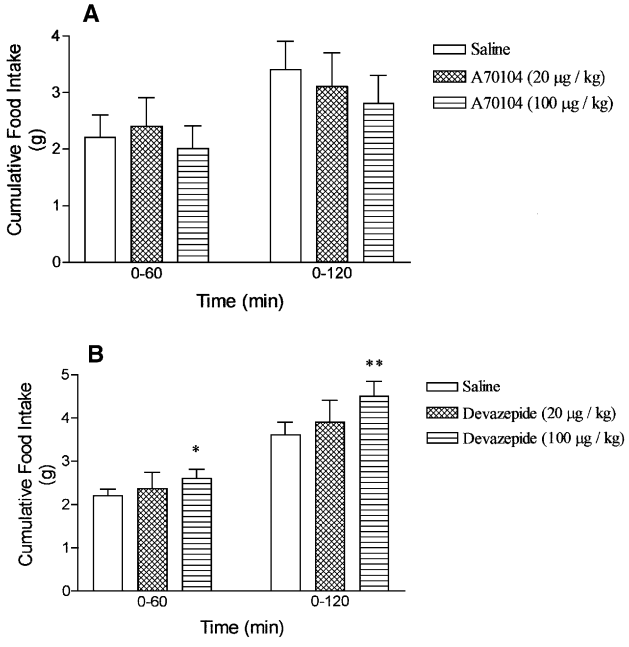

Fig. 2. Effects of (A) A70104 and (B) devazepide on food intake in 6-h-fasted rats. (A) The rats ($n=8$) were injected with vehicle or A70104 (20 or 100 μg/kg, i.p.) and food intake was measured during the 120-min test period. (B) The rats ($n=8$) were injected with vehicle or devazepide (20 or 100 μg/kg; i.p.) and food intake was measured during the 120-min test period. Vertical lines represent ± S.E.M. *$P<0.05$, **$P<0.01$.

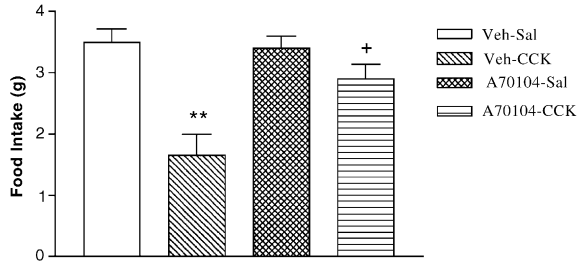

Fig. 3. Effect of A70104 pretreatment on CCK-induced hypophagia. Rats ($n=8$) were pretreated with A70104 (50 μg/kg; i.p.) 30 min prior to intraperitoneal administration of CCK (5 μg/kg). Cumulative food intake was measured 30 min after the second injection. Vertical lines represent ± S.E.M. $^{**}P<0.01$ compared with vehicle–saline control, $^{+}P<0.01$ compared with vehicle–CCK.

differences amongst the trials. A70104 administration did not produce any overt abnormal behaviours in the animals.

3.2. Experiment 2. Effects of A70104 and devazepide on food intake in 6-h-fasted rats

The effects of A70104 (20 and 100 μg/kg, i.p.) on food intake in 6-h food-deprived rats are shown in Fig. 2A. Both doses of A70104 did not significantly increase food consumption at any of the measurement intervals over the 120-min test period. By contrast, devazepide (20 and 100 μg/kg, i.p.) produced a dose-related increase in food consumption (see Fig. 2B). The 20 μg/kg did not significantly increase feeding during the test period, whereas the 100 μg/kg significantly increased cumulative food intake at 60 min ($P<0.05$) and 120 min ($P<0.01$).

3.3. Experiment 3. Effect of A70104 pretreatment on CCK-induced hypophagia

The results are illustrated in Fig. 3. Statistical analysis of the data showed that there were significant effects of drug treatment on food intake ($F_{(3,21)}=17.7021$, $P<0.01$ at 30 min). Post hoc tests revealed that while CCK (5 μg/kg, i.p.) significantly decreased cumulative food intake 30 min after administration ($P<0.01$), pretreatment with A70104 (50 μg/kg) abolished the depressant effect of CCK on feeding. A70104 had no effect on food intake on its own.

4. Discussion

It has been previously demonstrated in this laboratory that the CCK_1 receptor antagonist devazepide increases food intake in rats during a test meal following an oral preload (Ebenezer and Baldwin, 1995). In the present study, the effects of the CCK_1 receptor antagonists A70104, which is unlikely to penetrate the blood–brain barrier (Ebenezer and Parrott, 1993), was investigated on food consumption using a similar experimental protocol (Experiment 1). The results obtained show that A70104 had no effect on food intake in the rats when administered 30 min prior to a 4-h test meal. We have previously argued that oral preload experiments have the merit that if endogenous peripheral CCK is a satiety factor, then a CCK receptor antagonist should block (a) the satiating effects of CCK released during the first meal and, therefore, increase the size of the second meal, and (b) block the satiating effects of CCK released during the second meal and further increase the size of the second meal (Ebenezer and Baldwin, 1995). In order to extend these observations to another feeding model, Experiment 2 was undertaken in 6-h-fasted rats. The results obtained show that while the CCK_1 receptor antagonist devazepide (100 μg/kg) increased cumulative food intake during the 2-h test meal, A70104 (20 and 100 μg/kg) did not affect food consumption. It is interesting to note that other workers have used similar experimental protocols, where the animals were deprived of food for short periods of time, and they reported increases in food consumption with devazepide (see Smith and Gibbs, 1992, 1994; Baldwin et al., 1998).

The results obtained in Experiment 3 show that pretreatment of rats with A70104 abolishes the inhibitory effects of intraperitoneally administered CCK on food intake in 22-h-fasted rats. These results are in agreement with previous results obtained with A70104 in rats (Asin et al., 1992a,b), and confirm that peripherally acting CCK acts on CCK_1 receptors to inhibit food intake in rats (Hewson et al., 1988; Ebenezer et al., 1990; Weller et al., 1990; Smith and Gibbs, 1992). The dose of A70104 used in this experiment (i.e. 50 μg/kg) was in the middle of the dose range used in Experiment 1, and indicate that the doses of A70104 used in Experiments 1 and 2 would have been sufficient to block the effects of endogenously released peripheral CCK and increase food intake during the test meals if endogenous peripheral CCK acts as a satiety factor. The observation that A70104 does not increase food intake argues strongly against the hypothesis that endogenous peripheral CCK plays an important role as a satiety factor in rats.

The results of the present study confirm and extend to a rodent species those obtained with A70104 in pigs (Ebenezer and Parrott, 1993). These workers demonstrated that systemic administration of A70104 did not increase food intake in pigs and concluded that peripheral CCK is unlikely to play an important role in satiety. This view was further strengthened by the observations that systemic administration of 2-NAP, a CCK_1 antagonist which does not cross the blood–brain barrier (Baldwin et al., 1994), did not increase food intake in either pigs (Baldwin et al., 1994) or rats (Ebenezer and Baldwin, 1995; Patel and Ebenezer, 2000).

On the other hand, it is well documented that systemic administration of the CCK_1 receptor antagonist devazepide increases food consumption in a wide variety of animal species (Hewson et al., 1988; Ebenezer et al., 1990; Wolkowitz et al., 1990; Covasa and Forbes, 1994). These findings have provided the strongest support for the CCK-satiety hypothesis. However, as devazepide readily enters the brain from the circulation, it is possible that peripherally admin-

istered devazepide increases food intake by a central mode of action (Ebenezer and Baldwin, 1995; Baldwin et al., 1998). Recent studies in rats and pigs have shown that intracerebroventricular (i.c.v.) administration of devazepide, at doses that are too low to be effective when given systemically, increases food intake in these animals (Baldwin and de la Riva, 1992; Ebenezer, in press). In addition, if endogenous peripheral CCK is indeed a satiety factor that signals brain mechanisms involved in the control of feeding behaviour by way of the vagus (see Introduction), then the hyperphagic effect of devazepide should be abolished in vagotomised animals. Reidelberger (1992) tested this possibility by administering devazepide to control rats and rats that had received bilateral subdiaphragmatic vagotomies. He found that the 3-h cumulative intake of solid food after devazepide was increased by 25% and 35% in control and vagotomised rats, respectively. These results, therefore, indicate that devazepide can increase food intake by a mechanism that is independent of abdominal vagal innervation, and as the CCK_1 receptor antagonist can penetrate the blood–brain barrier, it is feasible that it acts centrally to increase feeding.

The results of this study have shown that systemic administration of a peripherally acting CCK receptor antagonist, A70104, does not stimulate food intake in rats. Similar results have also been reported in pigs with A70104 (Ebenezer and Parrott, 1993) and pigs and rats with 2-NAP (Baldwin et al., 1993; Ebenezer and Baldwin, 1995). As comparable results have now been obtained with peripherally acting CCK_1 antagonists in two different mammals, these findings provide strong evidence against the view that endogenous peripheral CCK plays an important role as a satiety factor. Furthermore, the demonstration that intracerebroventricular administration of A70104 to pigs (Ebenezer and Parrott, 1994) and devazepide (Ebenezer, in press) and 2-NAP to rats (Ebenezer, unpublished results) increase food intake suggests that if CCK has a role in the regulation of food intake, then it is brain CCK that is important (see Baldwin, 1992; Baldwin et al., 1998; Blevins et al., 2000; Ebenezer, in press) and not peripheral CCK, which may play a minor role by delaying gastric emptying (Moran and McHughes, 1988).

References

Anika, S.M., Houpt, T.R., Houpt, K.A., 1981. Cholecystokinin and satiety in pigs. Am. J. Physiol. 240, R310–R318.

Asin, K.E., Bednarz, L., Nikkel, A.L., Gore Jr., P.A., Montana, W.E., Cullen, M.J., Shiosaki, K., Craig, R., Nadzan, A.M., 1992a. Behavioral effects of A71623, a highly selective CCK-A agonist tetrapeptide. Am. J. Physiol. 263, R125–R135.

Asin, K.E., Gore Jr., P.A., Bednarz, L., Holladay, M., Nadzan, A.M., 1992b. Effects of selective CCK receptor agonists on food intake after central or peripheral administration in rats. Brain Res. 571, 169–174.

Bado, A., Roques, B.P., Lewin, M.J.M., Martinez, J., 1988. Cholecystokinin suppresses food intake in cats: structure–activity characterization. Pharmacol. Biochem. Behav. 31, 297–303.

Baldwin, B.A., 1992. CCK-8S as a putative satiety factor in farm animals. In: Dourish, C.T., Cooper, S.J., Iversen, S.D., Iversen, L.L. (Eds.), Multiple Cholecystokinin Receptors in the CNS. Oxford Univ. Press, Oxford, pp. 206–221.

Baldwin, B.A., de la Riva, C., 1992. Effect on food intake in pigs of antagonists acting on cholecystokinin type A and B receptors. J. Physiol. (Lond.) 446. 291 pp.

Baldwin, B.A., de la Riva, C., Gerskowitch, V.P., 1994. Effect of a novel CCKA receptor antagonist (2-NAP) on the reduction in food intake produced by CCK-8S in pigs. Physiol. Behav. 55, 175–179.

Baldwin, B.A., Parrott, R.F., Ebenezer, I.S., 1998. Food for thought: a critique on the hypothesis that cholecystokinin is a physiological satiety factor. Prog. Neurobiol. 55, 477–507.

Blevins, J.E., Stanley, B.G., Reidelberger, R.D., 2000. Brain regions where cholecystokinin suppresses feeding in rats. Brain Res. 860, 1–10.

Chang, R.S.L., Lotti, V.J., 1986. Biochemical and pharmacological characterization of an extremely potent and selective non-peptide cholecystokinin antagonist. Proc. Natl. Acad. Sci. U. S. A. 83, 4923–4926.

Covasa, M., Forbes, M.J., 1994. Effects of the CCK-8S receptor antagonist MK-329 on food intake in broiler chickens. Pharmacol. Biochem. Behav. 48, 479–486.

Crawley, J.N., Corwin, R.L., 1994. Biological actions of cholecystokinin. Peptides 15, 731–755.

Ebenezer, I.S., 1990. The effect of intracerebroventricular administration of baclofen on food intake in rats. NeuroReport 1, 73–76.

Ebenezer, I.S., 2002. Effects of intracerebroventricular administration of the CCK_1 receptor antagonist devazepide on food intake in rats. Eur. J. Pharmacol. 441, 79–82.

Ebenezer, I.S., Baldwin, B.A., 1991. Different effects of cholecystokinin (CCK-8S) on the electroencephalogram (EEG) of unanaesthetised rats and sheep. Br. J. Pharmacol. 104. 232 pp.

Ebenezer, I.S., Baldwin, B.A., 1995. 2-Naphthalenesulphanyl-L-aspartatyl-2-(phenethyl)amide (2-NAP) and food intake in rats: evidence that endogenous peripheral CCK does not play a major role as a satiety factor. Br. J. Pharmacol. 116, 2371–2374.

Ebenezer, I.S., Parrott, R.F., 1993. A70104 and food intake in pigs: implications for the CCK-8S satiety hypothesis. NeuroReport 4, 495–498.

Ebenezer, I.S., Parrott, R.F., 1994. Intracerebroventricular (ICV) administration of the CCK-A receptor antagonist A70104 increases food intake in pigs. Br. J. Pharmacol. 112. 331 pp.

Ebenezer, I.S., de la Riva, C., Baldwin, B.A., 1990. Effects of the CCK-8S receptor antagonist MK329 on food intake in pigs. Physiol. Behav. 47, 145–148.

Falasco, J.D., Smith, G.P., Gibbs, J., 1979. Cholecystokinin suppresses sham feeding in the rhesus monkey. Physiol. Behav. 23, 887–890.

Gibbs, J., Young, R.C., Smith, G.P., 1973. Cholecystokinin decreases food intake in rats. J. Comp. Physiol. Psychol. 84, 448–495.

Hewson, G., Leighton, G.E., Hill, R.G., Hughes, J., 1988. The cholecystokinin receptor antagonist L364,718 increases food intake in the rat by attenuation of the action of endogenous cholecystokinin. Br. J. Pharmacol. 93, 79–84.

Hull, R.A.D., Shankley, N.P., Harper, E.A., Gerskowitch, V., Black, J.W., 1993. 2-Naphthalenesulphanyl-L-aspartyl-(2-phenethyl)amide (2-NAP)—a selective cholecystokinin CCK-$8S_A$-receptor antagonist. Br. J. Pharmacol. 108, 734–740.

Inui, A., Okita, M., Inoue, T., Sakatani, N., Oya, M., Morioka, H., Ogawa, T., Mizuno, N., Baba, S., 1988. Mechanisms of action of cholecystokinin octapeptide on food intake and insulin and pancreatic polypeptide release in dog. Peptides 9, 1093–1100.

Kissileff, H.R., Pi-Sunyer, F.X., Thornton, J., Smith, G.P., 1981. C-terminal octapeptide of cholecystokinin decreases food intake in man. Am. J. Clin. Nutr. 34, 154–160.

Moran, T.H., McHughes, P.R., 1988. Anatomical and pharmacological differentiation of pyloric, vagal and brainstem cholecystokinin (CCK) receptors. In: Way, R., Schoenfeld, R. (Eds.), CCK Antagonists. Alan R. Liss, NewYork, pp. 117–132.

Moran, T.H., Ameglio, P.J., Peyton, H.J., Schwartz, G.J., McHugh, P.R., 1993. Blockade of type A, but not type B, CCK-8S receptors postpones satiety in rhesus monkeys. Am. J. Physiol. 265, R620–R624.

Morley, J.E., 1987. Neuropeptide regulation of appetite and weight. Endocr. Rev. 8, 256–287.

Passaro, E., Debas, H., Oldendorf, W., Yamada, T., 1982. Rapid appearance of intraventricularly administered neuropeptides in peripheral circulation. Brain Res. 241, 335–340.

Patel, J.D., Ebenezer, I.S., 2000. Effect of 2-NAP on food intake in rats: implications for the cholecystokinin-satiety hypothesis. Br. J. Pharmacol. 129. 146 pp.

Pullen, R.G.L., Hodgson, O., 1987. Penetration of diazepam and the non-peptide L364,718 into rat brain. J. Pharm. Pharmacol. 39, 863–864.

Reidelberger, R.D., 1992. Abdominal vagal mediation of the satiety effects of exogenous and endogenous cholecystokinin in rats. Am. J. Physiol., R1354–R1358.

Savory, C.J., Gentle, M.J., 1980. Intravenous injections of cholecystokinin and caerulein suppresses food intake in domestic fowls. Experientia 36, 1191–1192.

Silver, A.J., Flood, J.F., Song, A.M., Morley, J.E., 1989. Evidence for a physiological role for CCK in the regulation of food intake in mice. Am. J. Physiol. 256, R646–R652.

Smith, G.P., Gibbs, J., 1992. The development and proof of the CCK-8S hypothesis of satiety. In: Dourish, C.T., Cooper, S.J., Iversen, S.D., Iversen, L.L. (Eds.), Multiple Cholecystokinin Receptors in the CNS. Oxford Univ. Press, Oxford, pp. 162–182.

Smith, G.P., Gibbs, J., 1994. Satiating effect of cholecystokinin. N.Y. Acad. Sci. 713, 236–241.

Weatherford, S.C., Chiruzzo, F.Y., Laughton, W.B., 1992. Satiety induced by endogenous and exogenous cholecystokinin is mediated by CCK-8S-A receptors in mice. Am. J. Physiol. 262, R574–R578.

Weller, A., Smith, G.P., Gibbs, J., 1990. Endogenous cholecystokinin reduces feeding in young rats. Science 247, 1589–1591.

Wolkowitz, O.M., Gertz, B., Weingartner, H., Beccaria, L., Thompson, K., Liddle, R.A., 1990. Hunger in humans induced by MK-329, a specific peripheral-type cholecystokinin receptor antagonist. Biol. Psychiatry 28, 169–173.