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Calcitonin Reduces Feeding in Man, Monkey and Rat

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PERLOW, M. J., W. J. FREED, J. S. CARMAN AND R. J. WYATT. *Calcitonin reduces feeding in man, monkey and rat.* PHARMAC. BIOCHEM. BEHAV. **12**(4) 609–612, 1980.—It is proposed that calcitonin is a hormonal mediator of the satiety reflex. To test this hypothesis, effects of calcitonin on feeding and drinking were measured in rats and in rhesus monkeys. In monkeys, calcitonin produced severe (90%) and prolonged (3–5 days) reduction in feeding, and smaller decreases in drinking. In rats calcitonin decreased feeding in a dose-related manner over 24 hours, but increased drinking and urine output. A modest loss in body weight (2%) was also observed in psychiatric patients given calcitonin. It is suggested that calcitonin reduces feeding either through its effects on calcium metabolism, or by a direct action on the central nervous system.

Calcitonin Feeding Drinking Urination Satiety Weight loss

IT HAS been suggested that hormonal factors secreted by the gastrointestinal tract may signal satiety following a meal [30, 31, 45]. In humans, there is a post-prandial increase in the plasma concentration of cholecystokinin-pancreozymin, glucagon, secretin and gastrin [51,52]. All of these hormones stimulate the thyroid to secrete calcitonin (CT) [3, 7, 12, 14, 15, 19, 43, 50]. Cholecystokinin, glucagon [1, 24, 49] and another gastrointestional hormone, enterogastrone [45], have been found to reduce food intake in animals and man. Since there is a post-prandial increase in plasma CT [40,51], it seemed possible that the satiety effects of gastrointestinal hormones are mediated by CT. We therefore tested CT in rats and monkeys to determine if CT would, in fact, reduce feeding.

METHOD

Male Sprague-Dawley rats (350–550 g) (n=24) were acclimatized to individual metabolic cages for three days prior to the experimental period. For the following five days their daily urine volume, fecal excretion (as measured by number of fecal pellets), water intake and food intake (pelleted Purina Rat Chow) were measured and recorded. On the beginning of the third of these five days, synthetic salmon CT (Armour, Chicago, IL) was administered subcutaneously (0.0, 12.5, 25 or 50 MRC units/kg in a volume of 1 ml/kg). The dosage given to each rat was selected randomly with each rat being used only once (0.0 units; 12.5 units; 25.0 units; 50.0 units, with n=6 at each drug dose).

Male rhesus monkeys (5.5–7.0 kg) who had previously adapted to primate restraining chairs were used [39]. The animals were given food pellets (Purina Monkey Chow), half of an apple and water on a daily basis. The amount of food they ate during each 24-hr period was measured and recorded. Because it takes 3–4 weeks for a monkey to adapt to the chronic restraint of a primate chair [39], we were not able to weigh the monkeys immediately prior to the experiment. Following two days of observation, the monkeys were given either 5 (n=4) or 30 (n=7) MRC units/kg of synthetic salmon CT subcutaneously. Of the three animals that received both doses of the compound, all received the smaller dose first and received the second dose one to two months later.

Retrospectively, data was analyzed on an unselected group of psychotic patients (n=9), to whom CT was administered in a therapeutic trial. The weights of the patients were measured one week prior to, 12–36 hr following, and one week following single subcutaneous injections of 2 MRC units/kg synthetic salmon calcitonin [16,17]. The patients received an equivalent volume of placebo treatment one week prior to and one week following CT administration.

RESULTS

The rat study (Fig. 1) demonstrated that CT produced a dose-related reduction in food intake and fecal excretion during the first 24-hr after the injection. This was accompanied by an increase in water intake and pronounced diuresis. There was a dose-related reduction in body weight during the first 24-hr (one-way analysis of variance for independant groups, $F=3.56, p<0.05$) so that at the 50 MRC units/kg dose there was a 3.2% weight loss. During the second 24 hours after the injection, body weight returned to control values. Food intake exceeded control values, and fecal excretion also tended to be elevated, but not significantly. Water intake and urine volume remained elevated.

In the monkey study (Fig. 2), CT (30 MRC units/kg) reduced both food pellet and water intake ($F=16.13$, $p<0.00001$ and $F=3.40$, $p<0.01$, respectively). This reduction lasted three days for food (Neuman Keul's test, $p<0.05$) and one day for water (Neuman Keul's test, $p<0.05$). During all the studies the monkeys continued to eat half of an apple per day. CT in the lower dose had no noticeable effect on eating or drinking.

In humans there was a slight but significant reduction in

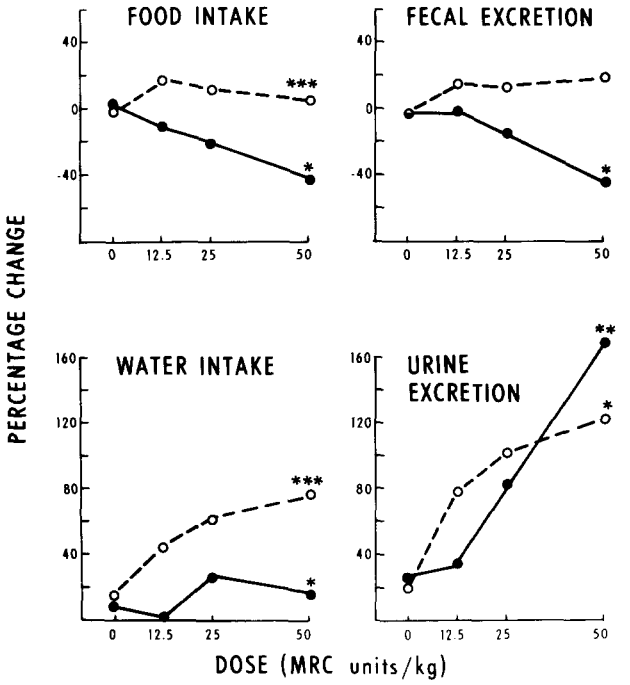

FIG. 1. Effect of subcutaneous calcitonin on feeding, drinking, urine volume and fecal excretion in rats. The solid line represents the change in feeding during the 24 hr following injection as compared to the mean of the two previous days. The dotted line represents the period from 24–48 hr after injection. One-way analysis of variance for independent groups $*p<0.005$, $**p<0.010$, $***p<0.050$.

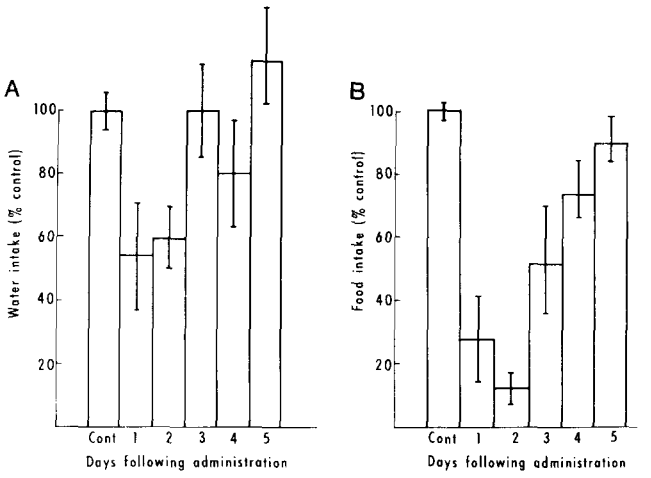

FIG. 2. Food pellet and water intake in rhesus monkeys following a single administration of calcitonin (30 MRC Units/kg., subcutaneously). Values are a percent of the mean (±SEM) of two pre-drug days (Cont.).

body weight during the immediate post-drug period as compared to the weeks before and after drug treatment (repeated measures analysis of variance for a single factor, $F=4.51$, $p=0.03$). Mean body weight 12 to 36 hours after CT was 2% less than one week later (paired t-test, $t=2.98$, $p<0.03$). There was no alteration in mean body when comparing CT treatment weights to weights obtained one week prior to drug administration. There was no response to the placebo injections.

DISCUSSION

In both monkeys and rats, CT reduced food intake. In monkeys, this reduction was large in magnitude and extraordinarily prolonged. In rats, the reduction was accompanied by a loss in weight, presumably secondary to decreased food intake and/or uncompensated urinary diuresis. The extent to which each of these processes contributed to the reduction in body weight in man remains to be determined. A volume diuresis accompanied by an increase in the excretion of sodium, calcium, magnesium and phosphate has been previously reported [2]. The mechanism by which this occurs is unknown. Based on observations presented here we are unable to determine the extent that the mild and evanesant CT-induced nausea (observed in about 10% of patients receiving 2 units/kg [Armour, product package information and Carman, unpublished data]) accounted for the weight loss in man and the decreased food intake in monkeys. In as much as the monkeys had only a modest reduction in drinking in the face of dramatic reduction in food pellet intake, we doubt that illness led to the reduction in eating. Furthermore, in another study (Freed, Perlow, Wyatt, submitted) using a conditioned adversion paradigm we demonstrated that CT does not induce measurable illness in rats, suggesting that reductions in feeding are not the result of illness or adversive effects of peptide, but rather a more specific property of the compound.

The major effects of CT are primarily on the skeletal, renal, and gastrointestinal organ systems [33]. Given in doses similar or slightly less than what we gave here to humans and rats, CT reduces the plasma concentration of calcium and phosphate, while increasing the urinary excretion of potassium, sodium, calcium, inorganic phosphate, hydroxyproline, and inorganic sulfate [2,33]. CT increases the secretion of water and electrolytes into the small intestine and has a variable effect on the intestinal absorption of calcium, the latter effect possibly via its action on vitamin D metabolism [33]. In therapeutic doses CT in humans decreases basal and stimulated gastric acid secretion and plasma gastrin [6, 9, 26]. While most mammalian studies have been performed in either non-primates or in humans, there is one study [8] in which a crude extract of porcine thyrocalcitonin was given to monkeys. In these animals the decrease in plasma calcium concentration was maximal 3 to 6 hr after subcutaneous administration, and lasted for more than 24 hours.

Within our present understanding of CT, it might be suggested that the reduction in feeding and drinking is the result of [1] a reduction in calcium and/or the calcium/sodium (Ca^{++}/Na^{++}) ratio in the brain, or [2] a direct action of CT on cells that control feeding and/or satiety in the central nervous system.

The first hypothesis is based on the work of Myers and others [4, 5, 35, 36, 47], who demonstrated that the intraventricular injection or intrahypothalamic application of Ca^{++} increased feeding in sheep, rats and pigs. On the basis of an apparent antagonism between Ca^{++} and Na^{++} ions [10], Myers suggested that the ratio of the two ions determined the "set point" for weight control and hunger [4,35]. Later, he and others [34,48] presented data indicating that the Ca^{++} and Na^{++} concentrations may also modulate the release of neurotransmitters known to influence ingestive behavior [25,27]. Extrapolating to the present situation, one would

expect that a reduction in plasma Ca^{++} concentration following the administration of CT would reduce feeding. However, it is questionable whether a reduction in plasma Ca^{++} would reduce brain Ca^{++} concentration to a degree sufficient to elicit satiety [29].

Because feeding is followed by cessation of feeding and a specific sequence of behavior that includes resting and/or sleeping, it has been postulated that after a meal, factors secreted by the intestine elicit this "satiety reflex" [30, 31, 45]. Cholecystokinin-panreozymin elicits this response, possibly by direct action on the brain [21,23], or, like secretin, gastin and glucagon, also released in association with meals, secondarily by stimulating the release of CT from C-cells. In rats, sampling at hourly intervals, the concentration of CT and gastrin became elevated 1–2 hr post-prandial [51]. A slightly delayed, but similar time course of concentration increases was observed in pigs [50]. Infusions of these gastrointestional peptides were immediately followed by increases in the plasma concentrations of CT [3, 7, 12, 14, 15, 19, 43]. Glucagon has been shown to reduce body weight and caloric intake in man [46]. Thus, we hypothesize that CT, or an active principle of CT [18], acts as a secondary factor in causing an animal to stop eating. Alcohol ingestion [53] and the intravenous injection of catecholamines [13, 28, 40] in experimental animals increases plasma concentration of CT. These elevated concentrations of CT may account for the anorexia associated with alcoholism, stress, coffee drinking [42] and smoking [20]. CT may do this by altering neuronal Ca^{++} [11, 38, 41] and electrolyte metabolism, and, thus, the release of neurotransmitters and putative neurotransmitters [44], or by direct action on CNS neurons that control feeding. This hypothesis is consistent with our knowledge of how other peptides of the APUD (amine precursor uptake and decarboxylation) system work—both through neuronal and non-neuronal effects [22, 32, 37].

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