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Weight Loss and Altered Circulating GI Peptide Levels of Rats Exposed Chronically to Nicotine[1]

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CHOWDHURY, P., R. HOSOTANI AND P. L. RAYFORD. *Weight loss and altered circulating GI peptide levels of rats exposed chronically to nicotine*. PHARMACOL BIOCHEM BEHAV **33**(3) 591–594, 1989.—This study was undertaken in male Sprague-Dawley rats to test the hypothesis that chronic ingestion of a low dose of nicotine supresses body weight gain. The results from this study suggest that chronic nicotine ingestion induces weight loss in rats without the loss of their food intake. To determine whether the nicotine-induced body weight reductions are associated with endocrinological changes, the levels of gastrin and CCK in plasma were measured by specific radioimmunoassays and were found significantly elevated during chronic ingestion of nicotine. The data indicate that reduction of body weight mass by nicotine might be dependent on both hormonal and metabolic factors.

Nicotine Weight loss Gastrointestinal peptides Gastrin CCK

NICOTINE, a major component of tobacco smoke, cigarettes and smokeless tobacco, has been shown to induce varieties of pathological disorders in humans and experimental animals (33, 34, 36, 37). Despite its known deleterious effects, the consumption of cigarettes by the world population in general has not been significantly decreased (34). Epidemiologic and cross-sectional studies suggested that intake of nicotine in the form of cigarette smoking results in decreased body weight gain (14,19) and it has also been shown that cessation of cigarette smoking by smokers results in increased body weight gain (6, 7, 29). The underlying mechanisms of the action of nicotine in regulation of body weight gain is unknown; however, studies on neuroendocrine reactivity of nicotine in smokers have shown that certain centrally-acting peptides (such as β-endorphin, arginine vasopressin, neurophysin, etc.) are released upon nicotine ingestion and cigarette smoking (27), but their role in regulation of weight gain has not been delineated.

Maintenance of body weight (energy balance) is the result of interaction of many factors. Aside from the influence of specific metabolites (glucose, amino acids) and hormones (insulin, glucagon), the role of opioids and cholecystokinin (CCK) have been studied in the regulation of food intake (3), but the implication of nicotine in CCK-mediated regulation of food intake has not been shown. To our knowledge, there have been no reported studies that shows the physiologic elevation of circulating levels of CCK or other gastrointestinal peptides associated with body weight gain. The current study was designed to determine the influence of chronic administration of nicotine on the levels of circulating CCK and other peptides relating to food intake and body weight gain.

METHOD

Twenty-four male Sprague-Dawley rats, eight weeks old and approximately 150 g body weight, were housed individually in stainless steel galvanized metabolic cages (7″ × 10″ × 7″) with 12-hr light/dark cycle. The animals were orally intubated daily at 9:00 a.m. for a total of 120 days via gavage tube with either saline or nicotine (20 μg/kg/day) in a volume of 1 ml of saline. The animals were allowed free access to food and to drinking water. The dose of nicotine for each animal was adjusted weekly according to changes in body weight. Food intake was measured by subtracting the amount of food left from the total amount provided. Food spillage was collected on absorbent papers placed underneath the mesh bottom cage and weighed, and this weight was subtracted from the actual amount of food left in food hampers. Body weight and food intake were monitored on alternate days using an electronic precision balance. Two weeks after the initiation of the experiment, the animals were fasted for 24 hr and mildly anesthetized with (0.1 mg/kg) of Ketamine (50 mg/ml) + acyl promace mixture. Two-milliliter blood samples were drawn from orbital sinus between 9 to 10:00 a.m. and placed in a chilled tube containing a mixture of heparin (10 U/ml) and trasylol (100 KIE/ml). The animals were returned to the cage

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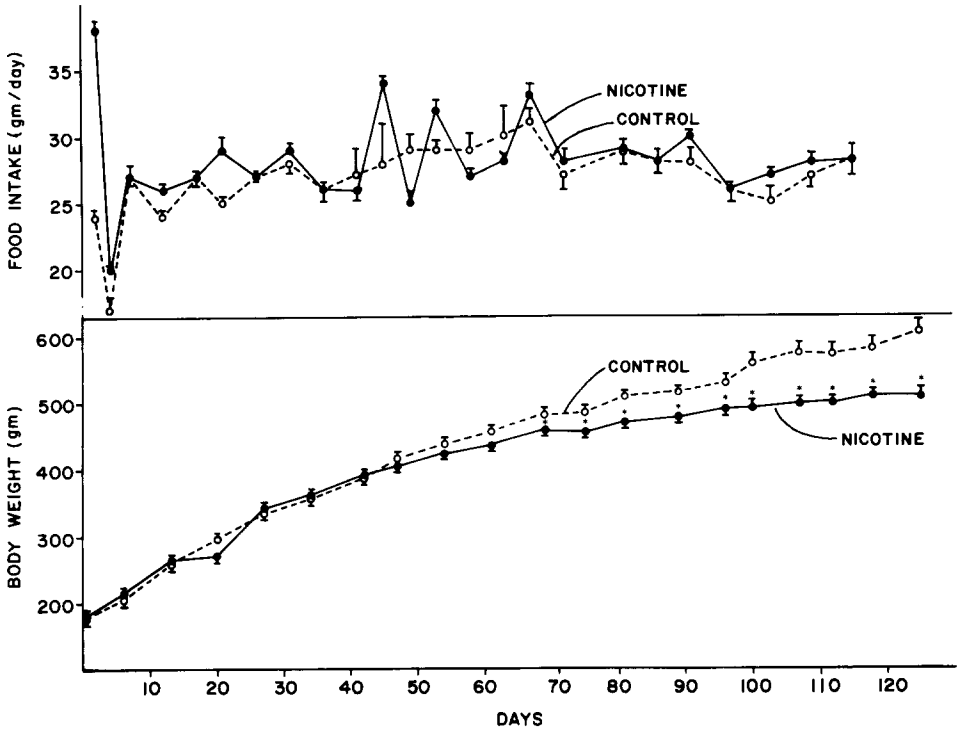

FIG. 1. Effect of chronic nicotine administration on the food intake (upper panel) and body weight (lower panel) of rats. ○—control (saline); ●—nicotine-treated.

following blood collection and were fully recovered from anesthesia within 30 minutes. At 17 weeks, the animals were fasted for 24 hr and blood samples were collected in the same manner and at the same time of the day as stated above. Plasma samples from two separate bleedings at 2 and 17 weeks were preserved at −20°C, and measured for gastrin and cholecystokinin in a single assay to avoid intraassay variation.

Plasma gastrin was measured by a specific radioimmunoassay using antiserum (UT-55). The gastrin radioimmunoassay used recognizes the C-terminal amino acid part of the gastrin molecule (21). In previous studies, we have shown that this antiserum measures gastrin in rat plasma (2).

Plasma CCK levels were measured by a specific radioimmunoassay (17,28). This assay was validated in dogs (17) and also in rats (2). The assay measures the release of CCK by food, and plasma levels of CCK in dogs have been correlated with exocrine pancreatic secretions (17).

The hormone concentrations were calculated as picomol per liter and expressed as mean ± standard error of the mean. Student's unpaired *t*-test and ANOVA were used to test the significance of differences between means. Differences with a *p*-value of less than 0.05 were considered statistically significant.

RESULTS

Figure 1 shows the food intake and weight gain of both control and nicotine-treated rats. The food intake in nicotine-treated animals (upper panel) was variable but consistent and was no different from the control group during the entire study period ($p>0.05$). Body weight gain of nicotine-treated groups (lower panel) remained consistent until 61 days of treatment and was not significantly different from control ($p>0.05$); however, the body weights between 68 to 120 days of nicotine treatment were found to be significantly lower ($p<0.05$) when compared to control group at the same time points.

Plasma gastrin and CCK levels measured at 2- and 17-week periods during chronic nicotine treatment are shown in Fig. 2. There was no significant changes in plasma levels of gastrin in control group at 2- and 17-week periods; however, plasma gastrin levels in nicotine-treated group (Fig. 2, left panel) were increased significantly from 47 ± 8 (pM) at two weeks to 92 ± 9 (pM) at 17 weeks, ($p<0.05$).

The plasma CCK levels in control groups at 2 and 17 weeks were not significantly different but the plasma CCK levels in nicotine-treated groups (Fig. 2, right panel) were found significantly increased from 81 ± 4 (at two weeks) to 106 ± 10 (pM) at 17 weeks ($p<0.05$).

DISCUSSION

The results from this study suggest that chronic nicotine administration by gavage feeding induced significant decrease in the body weight of rats without influencing the food intake (Fig. 1). Thus, reduction of the body weight gain observed in nicotine-treated rats appeared not to be associated with food intake (8). Several studies suggested that nicotine intake through cigarette smoking alters basal metabolism (4, 25, 26, 33) and increase enegy utilization (9, 13, 22, 32), thus contributing to the regulation of weight gain. In rats, hamsters and guinea pigs, nicotine administration resulted in reduction of weight with either no alteration in food intake (20, 23, 31) or with decrease in food consumption (35). The findings in these reported studies were attributed, in part, to age and gender differences (35). The data from our study agree with those reported by others (20, 22, 23, 25, 31) and suggest that nicotine induced reduction in weight gain may be related to increase in basal metabolism.

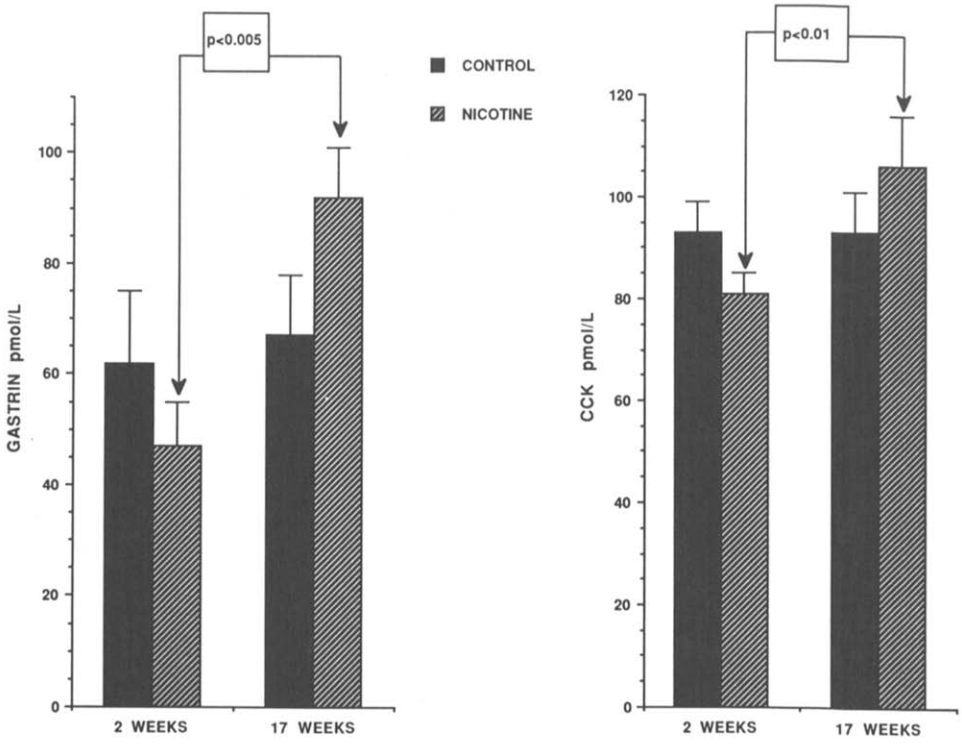

FIG. 2. Effect of chronic nicotine at 2 and 17 weeks on plasma levels of gastrin and CCK in rats. Open bars—control; hatched bars—nicotine-treated. $p<0.05$, significantly different from each other.

The reductions in body weight gain in animals administered with nicotine in the current study was accompanied by concomitant rise in plasma levels of CCK and gastrin (Fig. 2). The significance of this observation in the regulation of energy balance is not clear; however, evidence suggests that CCK, in contrast to gastrin, plays a major role in regulation of food intake in rats (1,4), but its chronic elevation did not appear to have reduced food intake. The changes in plasma levels of CCK and gastrin in nicotine-treated animals may be secondary to the local administration of nicotine.

It has also been shown that nicotine increases the release of catecholamines (24,31) and catecholamines have been shown to increase gastrin release (12,18). The elevated levels of gastrin, as found in this study, may have been induced by the increased secretion of catecholamines or by a direct effect of nicotine on the antral mucosa. In addition, gastrointestinal secretion and motility have been reported to be altered in smokers (10, 15, 16), which might affect nutrient absorption and circulating levels of CCK and gastrin.

The results from this study suggest that in addition to metabolic factors, regulation of body mass in nicotine-treated animals may be associated with chronic elevation of peptides of GI origin. More recently we have shown that rats given nicotine in drinking water for 16 weeks induced metabolic, hormonal and pathologic changes of the gastrointestinal tract and pancreas (11). The chronic elevation of these GI peptides in nicotine-treated animals probably reflect nicotine induced modulation of complex brain-gut interactions: this has yet to be determined.

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