Endocrine and Metabolic Regulation of Body Mass by Nicotine: Role of Growth Hormone

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ABSTRACT

This study was conducted in male Sprague Dawley rats, maintained chronically on drinking water and on nicotine water at nicotine concentrations of 0.31 and 1.23 mM, to determine the effect of nicotine on body weight regulation and circulating growth hormone levels. The study was repeated to determine the effect of nicotine withdrawal on the same parameters after exposing the animals to high dose of nicotine (1.23 mM) for 12 weeks and then removing the nicotine from water for four weeks. Growth hormone (GH) and insulin levels in the plasma were measured by sensitive radioimmunoassays. The results show that with nicotine treatment the body weight, food and fluid intakes in rats decreased significantly, concomitant with the decrease in plasma glucose and insulin levels while plasma growth hormone levels were increased significantly. A paired study conducted to determine the effect of decreased food intake showed no alteration of metabolic or hormonal parameters. Withdrawal of nicotine for four weeks reversed all of the previously noted parameters including plasma growth hormone levels; however, the body weights were not completely reversed. The data suggest that intake of nicotine affects body weights which appear to be associated with decreased plasma levels of glucose and insulin and release of growth hormone may play a role in that mechanism.

Introduction

Cigarette smoking and body weight gain in humans have been shown to be inversely related.8,12 Although this phenomenon may be linked to increased energy expenditure,1,12,16 the precise mechanism by which smoke components induces this effect, is unknown. Recent studies from our laboratory3,4 and also the studies reported by others7,15,16 have shown that nicotine, a component of cigarette smoke, plays a major role in the regulation of body weight gain. The objectives of our current study are (1) to determine whether or not nicotine from
smoking affects growth by a mechanism involving growth hormone release and utilization of metabolic regulators such as glucose and insulin, and (2) to determine whether decreased food intake but not nicotine, may be responsible for the regulation of weight gain in smokers.

Materials and Methods

Thirty-six male Sprague Dawley rats, six to eight weeks of age with a starting body weight 111 ± 2 g, were divided into four groups. Group I was maintained on tap water for 16 weeks (Control). Group II and Group III were maintained on tap water containing 0.31(NIC, 0.31mM) and 1.23(NIC, 1.23mM) mM nicotine respectively for 16 weeks; Group IV was maintained on tap water containing 1.23 mM of nicotine for 12 weeks, and, thereafter, the nicotine solution was replaced with tap water for an additional period of four weeks (NIC, 1.23mM + W). Throughout the 16 week period, body weights, food, and fluid intake in these animals were monitored at regular time intervals.

At the end of the 16 week period, the animals were fasted for 24 hr, anesthetized with a mixture of ketamine hydrochloride and acylpromace, and then sacrificed. Blood samples were collected in tubes containing heparin and trasylol mixture. Plasma was separated by centrifugation and stored at −20°C for measurements of hormones and glucose levels.

To determine that nicotine but not decreased food intake is responsible in growth retardation mechanism, a separate study was conducted in three groups of rats [Control (untreated), Nicotine (0.77mM) in drinking water and pair-fed (receiving the same amount of food consumed daily by nicotine group)] for 28 days. The doses of nicotine selected in this study were between high and low doses used for the chronic experiment. The blood samples were collected in the same manner after fasting for 24 hr and analyzed for plasma levels of glucose, insulin, and growth hormone.

Measurements

Plasma glucose was measured by the O-toluidine method. Plasma insulin was measured with specific insulin antibody using an insulin kit. Plasma growth hormone levels were measured by a specific radioimmunoassay.

Calculations

Growth hormone levels were represented as pg per ml and insulin levels as μU per ml. All data were calculated as mean ± S.E. ANOVA and student’s unpaired “t” test were used to determine the significant differences between the control and the treated groups. A p value of less than 0.05 was considered significant.

Results

The starting body weight of animals in all groups was 111 ± 2 g and increased gradually with time. Body weights, food and fluid intake, plasma levels of glucose, insulin, and growth hormone in both control and nicotine treated groups are shown in table I.

Body weights as well as food and fluid intakes decreased with nicotine intake with concomitant decrease in plasma glucose and insulin levels; however, the growth hormone levels in plasma were significantly elevated, and the increase

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† Developed in the laboratory of Dr. Thomas Badger, Professor & Director of Research, Department of Pediatrics, University of Arkansas Medical Sciences, Little Rock, AR.
Effect of Graded Doses of Nicotine on Metabolic and Hormonal Parameters

**GROWTH HORMONE AND BODY WEIGHT REGULATION BY NICOTINE**

### TABLE I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Nicotine (0.31 mM)</th>
<th>Nicotine (1.23 mM)</th>
<th>Nicotine (1.23 mM+W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>572 ± 28.1</td>
<td>486 ± 18.1*</td>
<td>393 ± 6.2*</td>
<td>448 ± 5.6†</td>
</tr>
<tr>
<td>Food intake (g/day)</td>
<td>27.7 ± 0.7</td>
<td>23.7 ± 0.3*</td>
<td>22 ± 0.6*</td>
<td>29.7 ± 1.5†</td>
</tr>
<tr>
<td>Fluid intake (ml/day)</td>
<td>41 ± 5.6</td>
<td>30 ± 1.8</td>
<td>22 ± 0.3*</td>
<td>49 ± 2.3†</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>141 ± 5</td>
<td>121 ± 6 *</td>
<td>105 ± 8 *</td>
<td>126 ± 5 †</td>
</tr>
<tr>
<td>Insulin (IU/ml)</td>
<td>37 ± 3</td>
<td>29 ± 3 *</td>
<td>27 ± 2 *</td>
<td>33 ± 3 †</td>
</tr>
<tr>
<td>GH (pg/ml)</td>
<td>261 ± 47</td>
<td>368 ± 77 *</td>
<td>655 ± 174 *</td>
<td>197 ± 19 †</td>
</tr>
</tbody>
</table>

*p < 0.05 significantly different from control.
†p < 0.05 significantly different between NIC (1.23 mM+W) and NIC (1.23 mM) group.
‡p < 0.05 significantly different between NIC (1.23 mM+W) and NIC (0.31mM) group.

in growth hormone levels were related to the doses of nicotine. The growth hormone levels measured after four weeks of nicotine withdrawal were not different from control (table I, column 4). Removal of nicotine from the drinking water reversed the food and fluid intakes and plasma glucose and insulin levels that were not significantly different from control. The body weights of rats, however, remained significantly lower after four weeks of nicotine withdrawal when compared to control.

To determine whether or not the decreased food intake by animals on nicotine may attenuate the body weight concomitant with metabolic and hormonal alterations, a pair-fed study was conducted for 28 days, and the results from that study are shown in table II.

Body weight gain, fluid intake, and glucose levels were significantly reduced in animals maintained on 0.77 mM nicotine in drinking water as compared to control (table II). Body weight gain in pair-fed groups was higher than in the nicotine group but significantly lower than in the control group. The food intake in both nicotine and pair-fed groups was identical; however, the fluid intake, glucose and insulin levels in pair-fed groups were significantly different from one another but not different from the control. Growth hormone levels were not significantly altered in any of the groups during 28 days of treatment (data not shown).

### Discussion

The results of this study show that nicotine ingested chronically via drinking water induced the decrease in body weight gain which is associated with concomitant decrease in plasma levels of glucose and insulin. This observation is attributed to nicotine induced metabolic alterations since withdrawal of nicotine reestablished the metabolic regulators to normal levels (table I). The data further extend this observation since it is shown that nicotine decreased body weight gain by decreasing food intake and fluid intake and not by altering glucose or insulin levels.

### TABLE II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Nicotine</th>
<th>Pair-fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>330 ± 8</td>
<td>298 ± 7*</td>
<td>303 ± 3</td>
</tr>
<tr>
<td>Food intake (g/day)</td>
<td>23 ± 0.02</td>
<td>21 ± 0.03*</td>
<td>21 ± 0.03*</td>
</tr>
<tr>
<td>Fluid intake (ml/day)</td>
<td>29 ± 0.02</td>
<td>17 ± 0.08*</td>
<td>28 ± 0.03†</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>135 ± 1.0</td>
<td>126 ± 1.1*</td>
<td>139 ± 2.0 *</td>
</tr>
<tr>
<td>Insulin (IU/ml)</td>
<td>16 ± 0.3</td>
<td>14 ± 0.5</td>
<td>17 ± 0.4 †</td>
</tr>
</tbody>
</table>

* *p < 0.05 significantly different from control.
†p < 0.05 significantly different between nicotine and pair-fed group.
show that nicotine intake decreases food intake allowing a possibility of nutritional deficiency which might influence the metabolic parameters. To circumvent that possibility, a pair-fed study was conducted. The results (table II) show that metabolic parameters were not altered with decreased food intake, suggesting that nicotine intake, but not food intake, is the prime mediator for metabolic alterations. In studies reported earlier, it has been shown that nicotine potentiates the energy expenditure.\textsuperscript{1,12,16} The results from our current study confirm those reported studies.

In addition to metabolic changes, significant changes were found in plasma levels of growth hormone with nicotine intake. The significance of these high levels of growth hormone in the growth retardation mechanism by nicotine cannot be fully explained. However, it has been shown that secretion of growth hormone occurs during smoking\textsuperscript{17} or nicotine ingestion\textsuperscript{5,17} and is attributed to stimulation of central cholinergic and adrenergic pathways\textsuperscript{2,11} since the use of alpha-adrenoreceptor blocking agents decreases the stimulated growth hormone levels.\textsuperscript{9} Our data suggest that chronic nicotine intake might have stimulated the central mechanisms\textsuperscript{13,14} that allowed the continuous secretion of growth hormone. The data further show that the secretion and maintenance of the level of growth hormone in circulation were nicotine dependent since withdrawal of nicotine reestablished the levels of growth hormone to basal (table I). Thus, it appears that in the regulation of body weight by nicotine treated animals required longterm administration of nicotine.

Based on our findings, it appears likely that secretion of growth hormone might have been enhanced by nicotine since the nicotinic effect on the central nervous system is known to be mediated through its interactions with nicotinic binding sites which are cholinergic in nature.\textsuperscript{10}

Acknowledgments

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References

8. DEPARTMENT OF HEALTH AND HUMAN SERVICES: The Health Consequences of Smoking: Nicotine


