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Nicotine from Cigarette Smoking Increases Circulating Levels of Cortisol, Growth Hormone, and Prolactin in Male Chronic Smokers

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Abstract. Results of this study indicate that nicotine from cigarette smoking increases circulating levels of cortisol, growth hormone, and prolactin in male chronic smokers. Previous studies have not addressed the question of whether the stimulus for smoking-related hormone release is the 'stress' of smoking or a pharmacologic action of nicotine and other tobacco substrates. Nicotine exposure is controlled in this study by allowing each subject to smoke only two 2.0 mg nicotine cigarettes during one experimental session and two 0.2 mg nicotine cigarettes in another session. Plasma levels of cortisol, growth hormone, and prolactin for the higher nicotine session were found to be significantly elevated over those for the low-nicotine session, indicating that nicotine itself plays a predominate role in smoking-induced hormone increases. All hormone levels for the 2.0 mg nicotine session had not returned to baseline 60 min after smoking.

Key words: Nicotine – Cigarette smoking – Cortisol – Growth hormone – Prolactin – Heart rate

Cigarette smoking has been demonstrated to increase circulating levels of corticosteroids and growth hormone in human subjects; there are no published reports on the effects of cigarette smoking on circulating prolactin levels. The literature is unclear whether the stimulus for smoking-related hormone release is the 'stress' of smoking or a pharmacologic action of nicotine and other tobacco substrates. This study was designed to control nicotine exposure while evaluating smoking-induced hormone release.

Serial blood samples were collected while chronic smokers smoked conventional and very low nicotine cigarettes. Circulating levels of cortisol, growth hormone (GH), and prolactin (PRL) were determined and these results compared with corresponding heart rate and circulating nicotine values.

Materials and Methods

Ten male chronic smokers (one pack per day or more of 1.0 mg nicotine cigarettes), 35–45 years of age and in good health, were recruited for a 2-day study beginning each morning at 8 AM. The subjects, inpatients at a social rehabilitation program at the Veterans Administration Medical Center in Brentwood, were drug-free and abstinent overnight from smoking, food, and beverages. A cannula was inserted into the basilic vein in the antecubital fossa and after a 30-min equilibration period, each subject smoked two United States Government research cigarettes (2.0 or 0.2 mg nicotine) within 10 min; none of the subjects experienced nausea. The order of nicotine administration was randomized.

During the 30-min baseline and for 1-h postsmoking, heart rate was monitored and serial blood samples were collected for circulating cortisol, GH, PRL, and nicotine. With the lighting of the first cigarette established as time zero, blood samples and radial pulse values were taken at −30, −15, 0, +10, 20, 30, 45, and 60 min. Plasma samples were stored at −20° C prior to nicotine and hormone analysis. Cortisol, GH, PRL, and nicotine were quantified using established homologous radioimmunoassay methods: cortisol (Ruder et al. 1972), GH (Schalach and Parker 1964), PRL (Sinha et al. 1973), and nicotine (Langone et al. 1973). Reagents for the GH and PRL assays were provided by the National Pituitary Agency; cortisol was obtained from Sigma, St. Louis, MO, USA. The intra-assay coefficient of variation for GH and cortisol is 4%, and the interassay coefficient of variation is 8%. The minimal detectable concentration is 0.1 ng/ml for GH, using as standard hgH batch HS2160E, and 0.1 μg/dl for cortisol. The intra-assay coefficient of variation for PRL is 5% and the interassay coefficient of variation is 10%; the minimal detectable concentration is 1.0 ng/ml, using as standard hPRL batch VLS-4.

An overall comparison of the 2.0 mg and 0.2 mg nicotine groups was made using 'repeated measures' analysis of variance (Winer 1971). The BMDP computer program P2V, "Analysis of Variance and Covariance Including Repeated Measures," was used to perform the calculations (Dixon and Brown 1979). The data for each of the five time periods (10 through 60 min) were transformed into the log of the difference between baseline and postsmoking values. The 'baseline' is defined as the average of the measures at −15 min and time zero.

Trends across time were analyzed separately for the 0.2 and 2.0 mg nicotine group because the variance of the measures were generally larger for the 2.0 mg nicotine group than those for the 0.2 mg nicotine group. Linear and quadratic trends across log time were determined using computer program P2V.

Results

The results of the analysis of variance indicate that significant differences exist between the nicotine and the very

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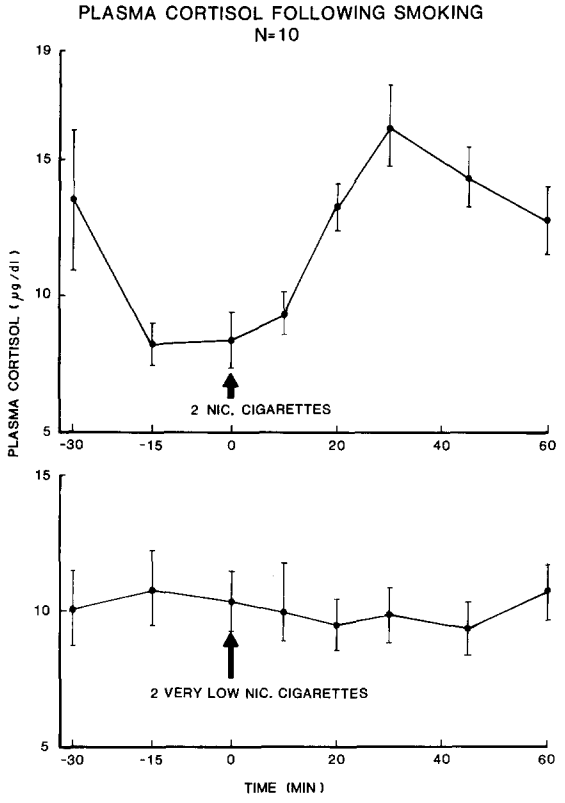

Fig. 1. Cortisol response to smoking nicotine and very low nicotine cigarettes in ten male chronic smokers (serial blood collection catheter inserted at −30 min). Mean ± SEM shown

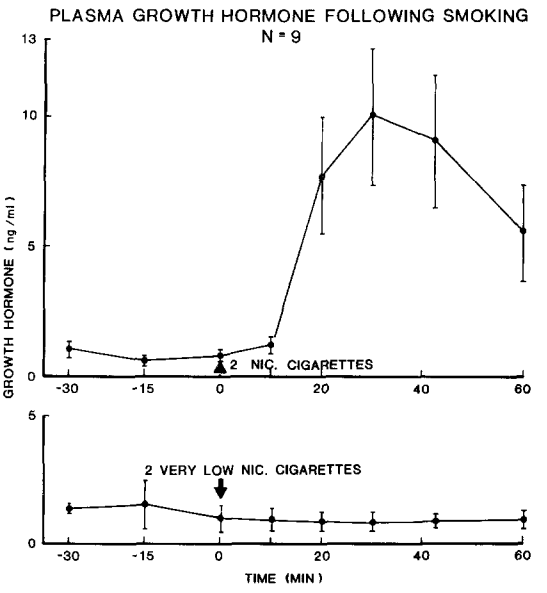

Fig. 2. Growth hormone response to smoking nicotine and very low nicotine cigarettes in nine male chronic smokers (serial blood collection catheter inserted at −30 min). Mean ± SEM is shown

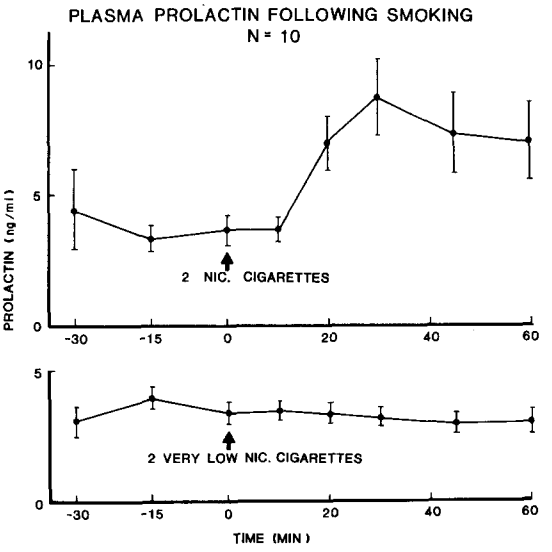

Fig. 3. Prolactin response to smoking nicotine and very low nicotine cigarettes in ten male chronic smokers (serial blood collection catheter inserted at −30 min). Mean ± SEM shown

low nicotine groups for plasma cortisol ($P < 0.0001$), GH ($P < 0.01$), and PRL ($P < 0.0001$).

When each of the experimental groups was analyzed separately for linear and quadratic trends across time, there were no significant trends for any measures in the 0.2 mg nicotine control group. For the 2.0 mg nicotine group, plasma cortisol increased 90% above baseline after 30 min (Fig. 1). The change from baseline at times +10, 20, 30, 45 and 60 min exhibited highly significant quadratic ($P < 0.00005$) and linear trends ($P < 0.02$). The mean plasma cortisol remained above baseline levels at time 60 min.

Mean plasma GH increased 12-fold above baseline at +30 min (Fig. 2). One subject was dropped from both the nicotine and very low nicotine groups because on both days he manifested large GH increases prior to smoking. We assume that the stress from placement of the intravenous cannula triggered the GH release in this subject. The overall time trend, including linear and quadratic, was highly significant ($P < 0.00005$). Mean plasma growth hormone remained elevated at time 60 min.

Plasma PRL exhibited an 150% increase for the 2.0 mg nicotine group 30 min after baseline (Fig. 3). The overall change across time was highly significant ($P < 0.00001$), while manifesting significant linear ($P < 0.03$) and quadratic trends ($P < 0.001$). Plasma PRL levels remained elevated at 60 min.

Smoking two 2.0 mg nicotine cigarettes resulted in a 25% increase of heart rate above baseline at 10 min following initiation of smoking (Fig. 4). After peaking, the heart rate exhibited a significant linear decrease through the 60-min test period ($P < 0.02$). By 60 min, the mean heart rate had almost returned to baseline.

For the 2.0 mg nicotine group, peak plasma nicotine levels were achieved at 10 min (Fig. 4); a linear decrease across the test period after this time was significant. Plasma nicotine levels remained elevated at 60 min.

Discussion

Previous studies have established a clear relationship between cigarette smoking and resultant increases in circulating cortisol and GH. In early work, Hokfelt (1961) demonstrated increases in plasma cortisol and urinary 17-hydroxycorticosteroids following cigarette smoking; Kershbaum et al. (1968)

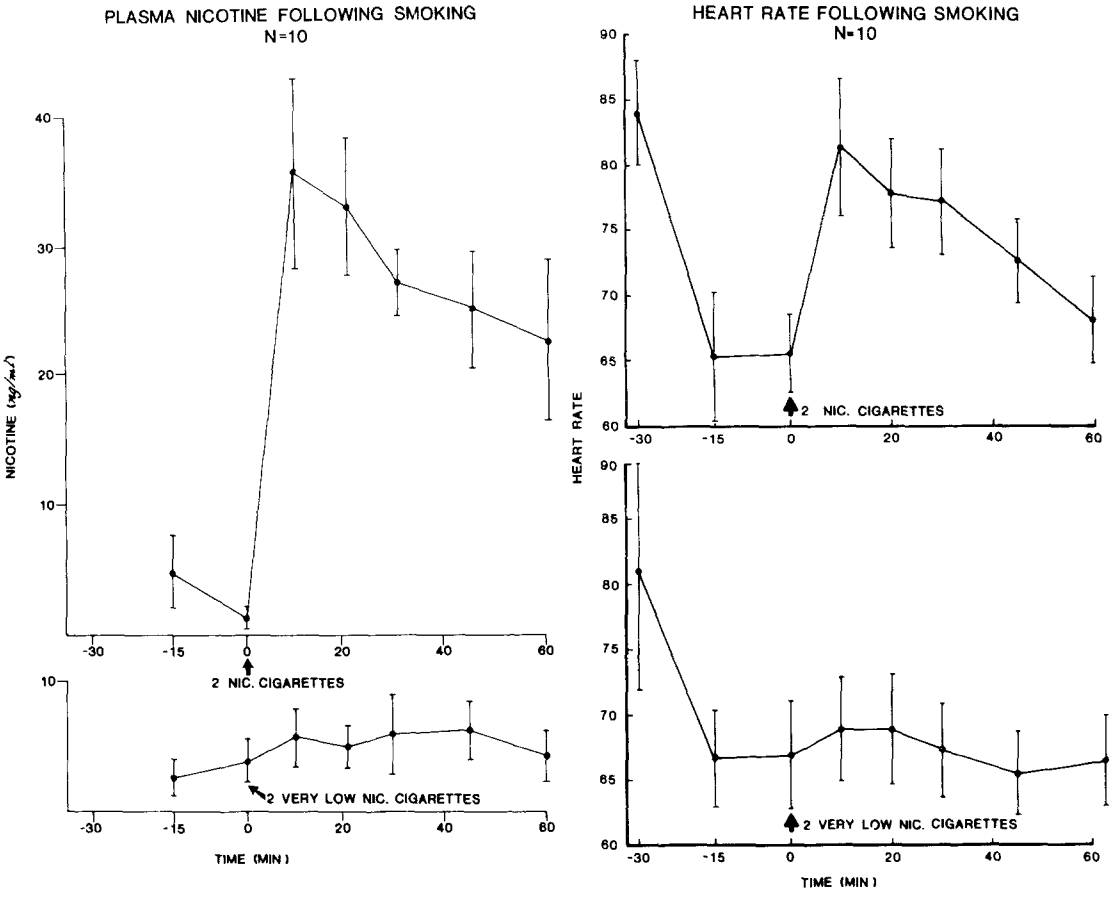

Fig. 4. Plasma nicotine levels and heart rate effects of smoking nicotine and very low nicotine cigarettes in ten male chronic smokers (serial blood collection catheter inserted at −30 min). Mean ± SEM shown

reported similar findings of smoking-related elevations of plasma 11-hydroxycorticosteroids. However, Tucci and Sode (1972) reported intact diurnal circadian variations of cortisol and unchanged 24-h 17-hydroxycorticosteroids during smoking. Despite these negative results, Cryer et al. (1976) and Winternitz and Quillen (1977) confirmed the findings of Hokfelt and Kershbaum.

In a study of ten young adult smokers, Sandberg et al. (1973) found plasma GH increased during smoking; these levels peaked at 30 min and remained elevated at 1 h. The authors speculated that rises in plasma GH might reflect a 'central' action of nicotine. Orsetti et al. (1975) in a study of smokers and nonsmokers reported plasma elevations of GH during 20 min of continuous smoking; thyroid stimulating hormone remained unchanged in the eight subjects studied. Cryer et al. (1976) and Winternitz and Quillen (1977) confirmed the findings of the previous studies; luteinizing hormone, follicle-stimulating hormone and testosterone also did not change from baseline (Winternitz and Quillen 1977).

We found no human studies in the literature describing the effects of cigarette smoking on circulating PRL levels. In a study of six normal subjects and eight persons with chronic hyperprolactinemia, plasma PRL levels were not altered by intravenous nicotine (Baumann et al. 1977); however, large doses of nicotine have been demonstrated to release PRL in lactating rats (Blake 1974). In this study we have shown that nicotine is the principal variable predicting smoking-induced elevations of circulating cortisol and GH; our results also demonstrate moderate increases in circulating PRL following smoking.

The mechanism for nicotine-induced increases in circulating levels of cortisol, GH, and PRL is most likely mediated through changes in hypothalamic cholinergic, catecholaminergic, or serotonergic neurons, which in turn modulate hypothalamic releasing and/or inhibiting factors; nicotine or neurotransmitters released by nicotine acting within the anterior pituitary is another possibility. We assume that the increased levels of circulating cortisol following smoking are secondary to increased anterior pituitary release of corticotropin (ACTH) rather than a direct adrenal cortical effect of nicotine.

Although adrenergic activity has been demonstrated to be causal in nicotine-mediated increases in rate and amplitude of contraction by the heart (Burn and Rand 1960), adrenergic mechanisms are probably not involved in the release of cortisol or GH by smoking. Cryer et al. (1976) found that infusion of phentolamine and propranolol did not alter smoking-induced cortisol secretion and had only a minor blunting effect on GH release. Central cholinergic actions of nicotine may in part explain the smoking-related increases in cortisol and GH, since Soulairac et al. (1977) reported that intravenous infusion of β-methylcholine produced increases in both circulating GH and cortisone in humans.

Nicotine-altered dopaminergic and/or serotonergic activity is most likely responsible for the increases in circulating PRL following smoking. Support for the hypothesis that

nicotine alters hypothalamic dopaminergic/serotonergic balance comes from the work of Goodman (1974), who demonstrated acute inhibition by nicotine of dopamine uptake in hypothalamic slices, but not in the striatum of the rat. In addition, Westfall et al. (1971) found that acute intraperitoneal injection of 1 mg nicotine significantly decreased the dopamine content of the rat caudate nucleus and increased the serotonin content at 30 min after injection.

Chronic alterations in hypothalamic and anterior pituitary functioning from multiple boluses of nicotine throughout the day may contribute to maintenance of the smoking 'habit'. Consistent with this speculation is research evidence supporting nicotine as a reinforcer of smoking behavior. Stollerman et al. (1972) found that when mecamylamine, a central acting nicotine antagonist, was administered to smokers, the rate of cigarette smoking increased by about 30% in laboratory tests. In parallel findings, Kozlowski et al. (1975) found that following smoking high nicotine cigarettes there were longer latencies to the next cigarette than when preceded by smoking low nicotine cigarettes.

Cigarette smoking behavior may be chemically reinforced by nicotine-induced release of endogenous substances, including ACTH and β-endorphin. Karras and Kane (1980) reported that 10 mg subcutaneous naloxone hydrochloride, which would presumably block the central actions of β-endorphin, reduced the amount of cigarettes smoked by chronic smokers by 32% over a 3-h period. Despite a recent report suggesting separate release mechanisms for ACTH and β-endorphin (Kalin et al. 1980), there is corresponding evidence indicating a close relationship between ACTH and β-endorphin secretion from the anterior pituitary (Guillermin et al. 1977; Rossier et al. 1977; Mains et al. 1977; Pelletier 1977; Weber et al. 1978; Kimura et al. 1979). Additional work is required to clarify a possible relationship between nicotine, ACTH, and β-endorphin.

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