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BRIEF COMMUNICATION

Pituitary Hormone Response to Cigarette Smoking[1]

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SEYLER, L. E., JR., O. F. POMERLEAU, J. B. FERTIG, D. HUNT AND K. PARKER. *Pituitary hormone response to cigarette smoking.* PHARMACOL BIOCHEM BEHAV **24**(1) 159–162, 1986.—Nausea was induced by having subjects smoke two high nicotine cigarettes in quick succession. Plasma levels of prolactin, adrenocorticotropic hormone, beta-endorphin/beta-lipotropin, growth hormone, arginine vasopressin, and neurophysin I increased without changes in thyroid stimulating hormone, luteinizing hormone, or follicle stimulating hormone. Nausea and pituitary hormone release correlated with high nicotine intake (smoking 2.87 mg nicotine cigarettes) but did not occur during lower nicotine intake (smoking 0.48 mg nicotine cigarettes). Individual differences in nausea and related hormonal responses may provide an objective method for predicting receptivity to smoking.

Adrenocorticotropic hormone Arginine vasopressin Beta-endorphin/beta-lipotropin Cortisol Follicle stimulating hormone Growth hormone Luteinizing hormone Nausea Neurohormones Neurophysin I Neuropeptides Nicotine Pituitary hormones Smoking Thyroid stimulating hormone

CIGARETTE smoking and nicotine administration have been shown to stimulate the release of several anterior and posterior pituitary hormones [2, 5, 17, 18], and the release of certain hormones has been related to the level of plasma nicotine during smoking [17]. Nausea induced by chair rotation [3] as well as by alcohol and apomorphine [13] and opioids [4], however, evokes a similar pattern of pituitary hormone release. An antiquated test for ruling out diabetes insipidus involved cigarette smoking [8], typically testing the functional release of arginine vasopressin (antidiuretic hormone) with doses of nicotine sufficient to induce nausea and emesis [1]. Such considerations raise questions of interpretation regarding the hormonal response to nicotine. Little progress has been made in discriminating between direct effects of nicotine and those secondary to nicotine-induced nausea. The present study is an attempt to delineate the pattern of pituitary hormone release associated with nicotine-induced nausea and to differentiate that pattern from the hormonal response to nicotine below the threshold of nausea.

METHOD

Subjects were 4 male smokers, mean age 36.5 years (±7.2 SEM), who smoked an average of 22.5 (±5.2 SEM) cigarettes per day. Subjects were recruited from the local community; they were in good general health and were not taking any medications. Subjects sat in an easy chair and watched a videotape movie on TV. Temperature was maintained at 21 (±1)°C and humidity at 50 (±5)%. Subjects were observed through a one-way mirror, and there were no interactions between subjects and the experimenter once the experimental session was underway. They were seated 30 cm from a console that signals the beginning and end of smoking periods. Experimental sequences and data acquisition were fully automated [10]. Standardized low (0.48 mg) and high (2.87 mg) nicotine research cigarettes (Tobacco and Health Research Institute, University of Kentucky) were used.

Sessions were 65 min long and consisted of a baseline period followed by the smoking of two cigarettes. Blood samples were drawn from the median antecubital vein of the subject's left arm using an indwelling scalp vein needle and a 1 meter length of heparinized tubing that extended to an adjacent room. Samples taken at 0, 10, 20, and 24.5 min from session onset define the baseline period; samples drawn at 30, 35, 40, 45, 50, 55, and 65 min define the response to the smoking stimulus. Blood was collected in heparinized plastic tubes, stored immediately in ice water, then centrifuged at 4°C and immediately separated; plasma was kept frozen at

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TABLE 1

UNITS, MEASUREABLE RANGE, INTERASSAY AND INTRA-ASSAY COEFFICIENTS OF VARIATION FOR ALL ASSAYS

Substance	Nicotine	Cortisol	ACTH	AVP	NSN	β-E/β-LPH	GH	PRL	TSH	LH	FSH
Units	ng/ml	μg/dl	pg/ml	pg/ml	ng/ml	pg/ml	ng/ml	ng/ml	μU/ml	ng/ml	ng/ml
Measureable Range	0.4–300	1–100	18–1200	4–400	0.2–100	20–2500	1–50	5–200	2.5–200	20–1500	20–1000
Interassay Coefficient of variation	6%	—	3.3%	10.1%	8.2%	8.6%	7.6%	4.2%	8.5%	8%	11%
Intra-assay Coefficient of variation	6%	8.4%	3.2%	5.3%	3.1%	6.3%	5.3%	—	—	4%	7%

−70°C or −20°C for subsequent cortisol, adrenocorticotropic hormone (ACTH), arginine vasopressin (AVP), neurophysin I (NSN), beta-endorphin/beta-lipotropin (β-E/β-LPH), growth hormone (GH), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and nicotine analysis.

Each subject participated in two sessions, in one of which they smoked two low nicotine cigarettes five minutes apart and in the other of which they smoked two high nicotine cigarettes in quick succession. Subjects were told to signal the experimenter if they experienced physical distress. All sessions were conducted at 1400 hr to minimize variation due to spontaneous ACTH secretion. Subjects were asked not to smoke cigarettes for 15 hours (overnight) prior to the study.

Assays

To minimize the effects of interassay variation, all samples from a given subject were analyzed in a single assay for each substance measured. Nicotine, cortisol, ACTH, AVP, NSN, β-E/β-LPH, LH, and FSH were measured in radioimmunoassays described in detail elsewhere [9, 15, 16]. The ACTH antibody did not crossreact with 1 μg/ml amounts of beta-endorphin, beta-lipotropin, enkephalins, parathyroid hormone, calcitonin, FSH, LH, PRL, TSH, or human GH. In the beta-endorphin/beta-lipotropin assay, there was less than 0.01% cross-reactivity with alpha-endorphin, alpha-melanocyte-stimulating hormone, methionine enkephalin, and leucine enkephalin; since the antibody exhibits equimolar cross-reactivity to beta-endorphin and beta-lipotropin, however, this asay reflects contributions from both neuropeptides. GH, PRL, and TSH were measured by radioimmunoassays utilizing National Pituitary Agency reagents. The units, measurable ranges, intra-assay and interassay coefficients of variation for all the assays are shown in Table 1.

RESULTS

Figure 1 shows nicotine and hormonal responses for the four subjects, comparing low nicotine conditions in which no indications of nausea were given, with high nicotine conditions in which nausea was reported. (Nausea was typically associated with paleness, sweating, and/or tachycardia.) Baseline plasma nicotine was low in both conditions, indicating compliance with instructions not to smoke overnight [10]. A series of directional hypotheses was tested within subjects using one-tailed paired *t*-tests: Plasma nicotine was

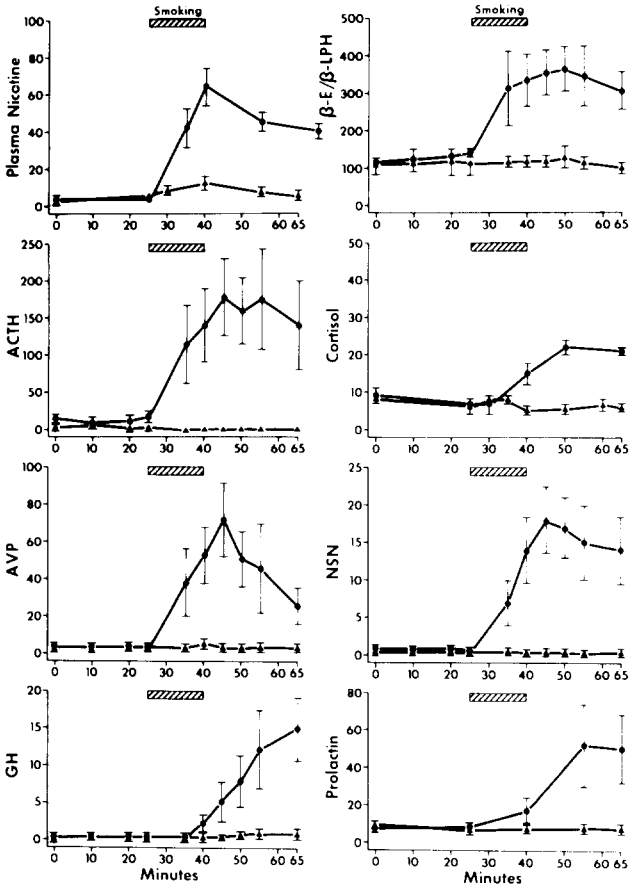

FIG. 1. Mean (±SEM) values for plasma nicotine and hormonal responses over time for four subjects; circles indicate the high nicotine condition and triangles the low nicotine condition. Units for each measurement are identified in Table 1. (ACTH—adrenocorticotropic hormone; AVP—arginine vasopressin; β-E/β-LPH—beta-endorphin/beta-lipotropin; GH—growth hormone; NSN—neurophysin).

significantly greater after the subjects smoked high nicotine cigarettes than after low nicotine cigarettes ($p<0.05$). Though lower compared with the high nicotine condition, mean plasma nicotine levels after smoking low nicotine ciga-

rettes (8.4 ng/ml) were significantly elevated over baseline levels (2.6 ng/ml) ($p<0.01$). The hormonal response pattern for the high nicotine condition revealed marked elevations in NSN, AVP, PRL, ACTH, β-E/β-LPH, and cortisol immunoreactivity after smoking; these levels were significantly greater than those reached after smoking low nicotine cigarettes ($p<0.05$). Although post-smoking GH levels in the high nicotine condition were significantly elevated over baseline ($p<0.05$), the post-smoking levels were not significantly different with respect to the low and high nicotine conditions. (GH levels were still rising, however, at the end of the sampling period.) For TSH, LH, or FSH (not shown in Fig. 1), post-smoking immunoreactivity levels were not significantly elevated over pre-smoking baselines, and no statistically significant differences in either pre-smoking baselines or post-smoking levels between high and low nicotine conditions were found for these neurohormones.

DISCUSSION

The hormonal response pattern to nicotine under conditions in which nausea does not occur has been described in previous reports from this laboratory [9,16]: in one study, nicotine levels and hormonal responses were integrated over time (area under the curve) to compare total biological activity; significant dose-response relationships between plasma nicotine and AVP, NSN, and β-E/β-LPH immunoreactivity were obtained [9]. In related research, significant nicotine-induced rises in cortisol immunoreactivity were found in the absence of measurable ACTH changes in smokers who reported no nausea; measurable increases in ACTH occurred only under conditions in which smokers reported nausea [16].

In the present study, when nausea occurred during smoking, a pronounced though still selective release of pituitary hormones was observed. The responses resemble the pattern of pituitary hormone release shown to accompany nausea and vomiting during rapid rotation [3] or drug administration [13]. This pattern of release includes ACTH, GH, and PRL elevations, in addition to the AVP, NSN, and β-E/β-LPH release also observed sub-nausea. The former may be characteristic of nausea rather than of smoking per se.

The neurochemical events that accompany nausea are thought to be coordinated by the brainstem emetic center. Numerous inputs into the emetic center evoke this activity, including stimulation from the adjacent chemoreceptor trigger zone, vestibular inputs, and vagus-nerve mediated gastric inputs [13,14]. Reports of nausea and vomiting in cancer patients who become ill in anticipation of chemotherapy also suggest stimulation from the cerebral cortex [6]. Nicotine is an emetic [1] and is most likely the critical ingredient in cigarette-induced nausea. The similarity in hormonal responses to nausea following smoking or motion sickness suggests that this effect of smoking is probably mediated indirectly through the emetic center rather than directly by the hypothalamus.

While this study suggests a well-defined pattern of hormone release associated with nausea induced by smoking, other studies have yielded some contradictions. Previous explorations of nausea induced by chair rotation [3] and drug administration [13] demonstrated increases in GH, AVP, PRL, and cortisol. In some research on pituitary hormones and smoking, however, the presence or absence of nausea was not ascertained [2, 5, 17]. Also, while AVP and NSN release has been shown to be correlated with nausea [12], occasional subjects have been reported to exhibit nausea and vomiting with no apparent hormone release [5]. Moreover, stimulation of cortisol, GH, and PRL by smoking has been observed in supposedly non-nauseated smokers [2, 17, 18], though plasma nicotine was measured in only one of these studies [17]. In our own research, we have demonstrated increases in cortisol immunoreactivity in non-nauseated subjects, but we found no accompanying ACTH increase [16], and have detected only minimal GH and PRL elevations in isolated instances.

These studies, taken as a whole, suggest that there is a need for careful, parametric investigation to tease out the factors controlling individual variability in the release of hypothalamic and pituitary hormones during nausea. Such research may also shed light on the mechanisms by which nicotine intake is regulated and smoking behavior reinforced [11]. It should be noted that the onset of nausea following the first smoking experience may be an important factor in discouraging some people from habitual smoking [7]. Thus, susceptibility to nausea induced by nicotine or by other substances that stimulate the emetic center may provide an index of receptivity to smoking, and the hormonal pattern elicited may constitute an objective indicator of these subjective effects.

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