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Effects of Heroin and Naltrexone on Plasma Prolactin Levels in Man

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ELLINGBOE, J., J. H. MENDELSON AND J. C. KUEHNLE. *Effects of heroin and naltrexone on plasma prolactin levels in man.* PHARMAC. BIOCHEM. BEHAV. 12(1) 163–165, 1980.—Plasma levels of prolactin were increased following intravenous self-administration of heroin by young men with a history of heroin addiction. Following 10 days of controlled heroin usage, tolerance could be demonstrated to the acute prolactin-releasing effect of heroin. There was no evidence that a single dose of naltrexone affected basal prolactin levels.

Prolactin Heroin Naltrexone Human Males Tolerance

FOLLOWING the initial reports of an acute prolactin-releasing action of morphine [5, 7, 21, 27], numerous studies have confirmed that opiate alkaloids and endogenous opioid peptides, as well as their analogues, stimulate prolactin secretion in male and female rats [1-4, 8, 10, 12, 15-17, 19, 10, 11, 12]. Preliminary reports indicate that such effects can also be found in goats [13] and monkeys[11]. Despite clinical symptoms which suggest that opiates might increase prolactin secretion in women, only one study has been described in which immunoreactive prolactin was measured in women after acute morphine administration [25]. Only one investigation of which we are aware has reported the effects of an opiate (an enkephalin analogue) on prolactin levels in normal men [24]. In two other studies, the effects of single doses of methadone were examined in methadone-dependent men. No significant alterations of plasma prolactin could be detected in one of these studies [6], while in the other, an average increase to only twice the basal plasma prolactin level was found [11].

Tolerance to the acute prolactin-releasing effect of morphine has been demonstrated in the rat [19]. But to date, the only indication of tolerance development in man is to be inferred from the relatively small or insignificant prolactin response reported in methadone-maintenance patients [6,11]

METHOD

Three healthy heroin-dependent males (Subjects 1, 2, 3—ages 25, 27 and 23—heroin use 7, 7 and 9 years) were observed under carefully monitored conditions in studies designed to assess the efficacy of naltrexone for the treatment of heroin addiction. Each man was given a complete physical and laboratory examination and no abnormal findings were found other than mild opiate withdrawal symptoms in all subjects upon admittance to the study on Day 1. Informed consent was provided by each subject before the studies were initiated.

All subjects were kept drug-free until Day 6, when catheters were inserted into arm veins for blood collection using portable non-thrombogenic constant-exfusion pumps. Plasma was prepared from integrated 30-min blood samples collected serially throughout the day. Heroin (10 mg IV) was self-administered at 1:30 p.m. on Day 6. On Day 8 the procedure was repeated identically. During a 10-day long period (Days 10–19), the subjects were permitted to self-administer heroin (10 mg per dose) four times a day, at 8:30 a.m., 2:30 p.m., 8:30 p.m. and 2:30 a.m. Subject 1 was given the narcotic antagonist naltrexone (50 mg PO) daily at 7:30 a.m., starting on Day 10 and continuing through the entire study. He elected to use heroin only three times during this period (twice on Day 10 and once on Day 17). Subjects 2 and 3 received naltrexone placebo and chose to self-administer 23 and 34 doses of heroin (mean=23 and 34 mg/day), respectively, during the heroin phase of the study. Blood was collected again on Day 19, while Subjects 2 and 3 injected heroin at the prescribed times of 8:30 a.m. and 2:30 p.m. Subjects 2 and 3 were then withdrawn using methadone—25 mg on Day 20 and progressively reduced to 5 mg on Day 24. Subjects 2 and 3 were opiate free for the remainder of the study. On the last blood collection day (Day 32), naltrexone (25 mg PO) was administered to Subjects 2 and 3 at 11:15 a.m.

Plasma prolactin was assayed in duplicate in each integrated 30-min plasma sample using a double antibody radioimmunoassay procedure and materials provided by the National Pituitary Agency, National Institute of Arthritis, Metabolism and Digestive Diseases. Results are expressed as nanograms VLS # 3 prolactin standard per milliliter of plasma. Intraassay coefficients of variation were 6.9% and 3.1% for samples in the 5–10 ng/ml range and 25–30 ng/ml ranges, respectively. Inter-assay coefficients of variation were 9.1% and 3.2% for control samples averaging 3.9 ng/ml and 26.8 ng/ml, respectively. Assay sensitivity was 3 ng/ml. All samples from an individual subject were analyzed in the same assay.

RESULTS

Following the injection of single 10-mg doses of heroin on

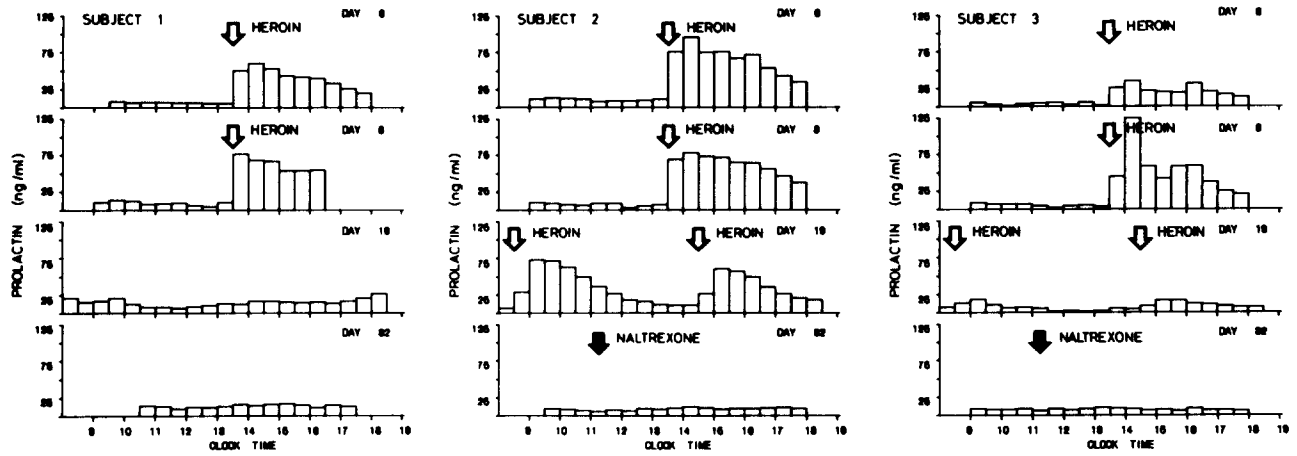

FIG. 1. Plasma prolactin levels before and after single doses of heroin (10 mg) in subjects in the drug-free state (Days 6 and 8) and heroin-dependent state (Day 19). Naltrexone (25 mg) was administered to Subjects 2 and 3 on Day 32, while Subject 1 was blocked by naloxone (50 mg/day) from Day 10 to the completion of the study.

Days 6 and 8, plasma prolactin rose rapidly from basal levels. Prolactin levels during the 3-hr period after heroin injection averaged 8.0±1.8 (SD) times the preadministration basal prolactin values. For Subject 1, mean plasma prolactin levels 0–3 hr after heroin were 48.1 ng/ml on Day 6 and 62.3 ng/ml on Day 8. Comparable values for Subject 2 were 77.1 ng/ml and 70.7 ng/ml, while prolactin concentrations for Subject 3 averaged 25.4 ng/ml and 66.4 ng/ml on Days 6 and 8, respectively.

When plasma levels were measured again after injection of single 10-mg doses of heroin in Subjects 2 and 3 (Day 19), following 9 days of regular heroin self-administration, there was evidence of a blunted prolactin response, especially in Subject 3. Mean prolactin levels during the two 3-hr periods following heroin injections at 8:30 a.m. and 2:30 p.m. were 76% and 60% of the mean values during the comparable period on Day 8 for Subject 2 and only 13% and 17%, respectively, for Subject 3.

In the case of Subject 1, who had been receiving daily naltrexone doses since Day 10, basal prolactin levels during Day 19 averaged 14.6 ± 4.8 ng/ml compared with basal (pre-heroin) levels of 6.9 ± 1.0 ng/ml and 9.7 ± 2.8 ng/ml on Days 6 and 8. After 12 additional days of continuous naltrexone administration, plasma prolactin levels averaged 13.7 ± 1.8 ng/ml on Day 32.

Subjects 2 and 3 received their first doses of naltrexone on Day 32. Following 25 mg of naltrexone there were no significant changes detectable in plasma prolactin levels. Pre-naltrexone prolactin levels were 7.9±1.7 ng/ml compared to 10.4±0.9 ng/ml after naltrexone for Subject 2, and 8.3±1.0 ng/ml, respectively, for Subject 3.

DISCUSSION

These data are consistent with findings reported by others [1-5, 7, 8, 10-13, 15-17, 19-25, 27] showing an acute prolactin-releasing effect of opiates. Administration of heroin to non-dependent heroin addicts was followed by rapid increase in plasma prolactin. The magnitude of the prolactin response varied somewhat among the three individuals studied, and was not entirely reproducible between Days 6 and 8 in the same subject. Such differences might be due to daily shifts in the sensitivity of this endocrine system, as is indicated by differences in the mean basal plasma prolactin levels from day to day. When calculated with respect to the pre-drug basal prolactin levels, the relative response to acute heroin administration was remarkably similar in all subjects.

Following 10 days of regular heroin use by two subjects, tolerance appeared to develop to the acute prolactin response. Subject 3, who had self-administered more heroin during the preceding 10 days than Subject 2, responded with less than twice the average of his earlier pre-drug basal prolactin levels. This small prolactin response to heroin is of the same magnitude that was reported in methadone-dependent men [11]. Muraki and Tokunaga [19] had found previously that high doses of morphine were necessary to demonstrate tolerance development in the rat. Differences in tolerance to the prolactin effect of heroin between Subjects 2 and 3 may reflect individual variance, or possibly a reflection of somewhat different heroin usage on Days 10–18.

In contrast to reported negative effects of naloxone on prolactin secretion in rats [2, 12, 17, 23], our data are similar to those of Janowsky *et al.* [14] in suggesting that in man the acute administration of a narcotic antagonist probably does not alter basal circulating levels of prolactin. More extensive unpublished data from studies with non-addict subjects in our laboratory also indicate that plasma prolactin is unaltered by single doses of naltrexone. Rats release prolactin following stress of experimental procedures (even handling) and naloxone has been shown to inhibit stress-induced prolactin secretion [26]. If opiate mechanisms are involved only in the stress mechanisms that augment prolactin release, one might not expect to observe reduced prolactin levels in humans following naltrexone administration under nonstressful circumstances. While finding no effect of naltrexone on prolactin levels in humans, we have been able to demonstrate a quite significant increase in plasma lutropin (LH) under the same conditions [18].

Both the acute and chronic effects of opiates on prolactin secretion are probably the consequence of altered hypothalamic dopamine activity. Opiates are known to act on dopamine systems, and methionine enkephalin has been found to increase the content of dopamine in the median

eminence of rats [10], indicating that dopamine release into the hypothalamic-pituitary portal capillaries is inhibited. Opiate suppression of dopamine release would reduce the inhibitory effect of dopamine on prolactin release at the pituitary. Although this appears to be the most parsimonious explanation for effects of opiates on prolactin, direct action of opiates at the pituitary level has been reported [9,16], although not replicated by others [1, 19, 22, 23]. Changes in dopamine activity within the hypothalamus may also alter prolactin secretion through effects on other putative prolactin releasing or inhibiting factors.

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