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Ergot Drugs Suppress Plasma Levels of Prolactin (PRL) but Not Growth Hormone (GH), Luteinizing Hormone (LH) or Corticosterone (CORT) in Parturient Mice

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MANN, M. A., S. D. MICHAEL AND B. SVARE. *Ergot drugs suppress plasma levels of prolactin (PRL) but not growth hormone (GH), luteinizing hormone (LH) or corticosterone (CORT) in parturient mice.* PHARMAC. BIOCHEM. BEHAV. 17(4) 837–840, 1982.—Plasma levels of prolactin (PRL), growth hormone (GH), luteinizing hormone (LH), and corticosterone (CORT) were measured in parturient Rockland-Swiss (R-S) albino mice following the daily administration for 10 days of 0.5 mg ergocornine (ERGO), 0.5 mg bromocriptine (BROMO), or sesame oil (OIL). The dams were provided with replete foster young on a daily basis so as to prevent the decline in suckling activity that normally occurs in undernourished pups of ergot-treated dams. Circulating PRL levels were significantly reduced by both ergot drugs but plasma levels of the other hormones measured were not altered. Thus, ergot drugs have relatively specific effects on PRL even in parturient animals receiving sustained high levels of suckling stimulation.

Prolactin Growth hormone Corticosterone Luteinizing hormone Ergot drugs Lactation Suckling

THE regulation of prolactin (PRL) secretion by pituitary-hypothalamic dopamine (DA) continues to be a topic of considerable attention in reproductive physiology. It is well known that DA directly inhibits both basal and suckling-induced levels of the hormone [2,15]. Ergot alkaloids, which act as DA receptor agonists [4], have been used to probe PRL secretory pathways [7, 8, 27]. Like DA, ergot drug administration in postpartum rodents has been shown in numerous studies to suppress PRL secretion and lactation by acting at both hypothalamic and pituitary levels (cf. [6, 9, 26, 29, 30]).

In spite of the above reports, two factors have prompted us to re-examine the effects of ergot drugs on postpartum PRL secretion. First, of the studies mentioned above, only a few have evaluated the PRL-inhibiting properties of these agents relative to alterations in circulating levels of other hormones (e.g., [20,29]). Because DA plays a vital role in the secretory activity of other pituitary hormones, especially the gonadotropins [5], an examination of the specificity of ergot drug effects would be important. Secondly, it is well known that postpartum PRL release is governed by suckling stimulation from young. High levels of plasma PRL are maintained by high levels of suckling stimulation while low PRL titers are observed in the absence of such stimulation [11]. Owing to deficits in lactation, pups of ergot-treated mothers become undernourished, weakened, and eventually die of starvation (e.g., [1]). They provide a qualitatively and quantitatively inferior suckling stimulus when compared to pups of untreated mothers. Therefore, ergot-mediated deficits in PRL secretion during the postpartum period may be due, in part, to indirect effects on suckling as opposed to direct effects on hypothalamic-pituitary DA.

The purpose of the present study was to assess the specificity of the suppressive effects of ergot drugs on circulating PRL. This was accomplished by measuring plasma levels of PRL, growth hormone (GH), luteinizing hormone (LH) and corticosterone (CORT) in ergot-treated parturient mice. Vigorous suckling stimulation was maintained in the dams by utilizing a fostering procedure in which the young were exchanged on a daily basis for replete, recently nursed pups.

METHOD

Animals

Nulliparous Rockland-Swiss (R-S) albino mice, 60–70 days of age, were mated with adult R-S males and checked daily for the presence of vaginal plugs. Inseminated females

were individually housed in 28×18×13 cm translucent cages and provided with food (Charles River Mouse Chow) and water ad lib. The animals were maintained at 23±1 °C on a 12/12 hr light/dark cycle with lights on between 0700 and 1900 hr. On the day prior to parturition (Gestation Day 18), the homecages of the females were modified so as to prevent them from receiving suckling stimulation prior to drug administration. A 0.6 cm wire mesh partition was placed inside each cage 3.8 cm above the floor so that delivered pups dropped through the wire screen. On the day of parturition (Postpartum Day 1) delivered pups and partition were removed and the dams were provided with cotton nesting material. The dams were weighed daily on Postpartum Days 1 through 10.

Drug Administration

On the day of delivery, dams were randomly assigned to one of three treatment groups. Separate groups of animals were given 0.5 mg of ergocornine hydrogen maleate (Group ERGO; N=14), or 0.5 mg of bromocriptine (CB-154; Group BROMO; N=13) or sesame oil (Group OIL; N=12). Ergot drugs were obtained from Sandoz Pharmaceuticals (East Hanover, NJ) and suspended in 0.1 ml of sesame oil. Animals were given a single subcutaneous injections of either ergot or an equal volume of the oil vehicle once a day at 1100 hr beginning on the day of delivery and continuing for ten consecutive days. This dose and duration of ergot administration was selected on the basis of its demonstrated effectiveness in suppressing plasma PRL in rodents [1,18].

Fostering Procedure and Assessment of Lactation

To ensure the viability of suckling stimulation a fostering procedure was instituted beginning on the third day following parturition, i.e., 48 hr following the initial injection. On Postpartum Day 3 and on a daily basis for 8 days, each dam was proferred 5 preweighed 1–4 day old foster pups obtained from untreated lactating R-S dams. Each day the foster pups were removed, weighed and exchanged for 5 more recently suckled preweighed pups. It is important to note that this technique for maintaining adequate levels of suckling stimulation has been routinely used in our previous research without compromising any aspect of maternal behavior in experimental dams [23]. An animal was scored as having lactated if one of three criteria was met: (1) the weight of foster young equalled or exceeded their prefostering weight on any given day; (2) the presence of milk bands in the pups' stomachs was noted on any given day; or (3) the presence of milk in the mammary glands was noted upon autopsy. Suckling stimulation was assessed by daily observations of nipples and noting the presence or absence of redness and distention. Informal observations were conducted to assess pup-directed maternal activities.

Radioimmunoassays

At 0900 hr on Postpartum Day 11 (i.e., 24 hr following the last injection) blood samples were obtained by cardiac puncture without anesthesia. Samples were centrifuged at 2400 rpm for 15 min and the sera aspirated and stored at −20°C. Prolactin and GH were measured by homologous assays [21,22]. Determinations were made on duplicate 10 μl aliquots of plasma for PRL and duplicate 20 μl aliquots for GH. Concentrations of LH were measured in duplicate 10 μl samples by a double antibody ovine-ovine LH assay [14] as verified for the mouse [3]. Single 20 μl samples were assayed for corticosterone [13]. Values for each hormone are expressed as ng of the respective standard as previously described [12]. Hormone concentrations determined in duplicate were averaged and median values were computed for each treatment group.

TABLE 1

MEDIAN PLASMA LEVELS (ng/ml) OF PROLACTIN (PRL), GROWTH HORMONE (GH), LUTEINIZING HORMONE (LH), AND CORTICOSTERONE (CORT) IN PARTURIENT R-S MICE FOLLOWING THE DAILY ADMINISTRATION OF ERGOCORNINE (ERGO), BROMOCRYPTINE (BROMO), OR SESAME OIL (OIL)

Group	N	PRL	GH	LH	CORT
OIL	12	196.4	12.8	46.5	15.0
ERGO	11	19.4*	16.0	45.0	17.0
BROMO	13	21.6*	8.5	40.5	19.5

*Significantly different from Group OIL, $p<0.01$.

Data Analysis

Plasma hormone values were not normally distributed and were therefore analyzed by Kruskal-Wallis Analysis of Variance [19]; individual group comparisons were made using the Mann-Whitney U test. Mean pup weight change was analyzed by ANOVAs and post-hoc Honestly Significant Difference (HSD) tests [28].

RESULTS AND DISCUSSION

Animals were eliminated from the experiment if cannibalization of an entire litter was evident on three consecutive days. Three ergocornine-treated animals cannibalized young and their data were excluded from the analyses, leaving 11 animals in this group. Regardless of the treatment condition, all remaining animals (N=36) received suckling stimulation and exhibited normal maternal caretaking activity (i.e., retrieval of strayed young, nest-building and assumption of nursing postures). It is important to note that all animals were observed to be in a nursing posture over their young and receiving suckling stimulation at the time of blood collection.

Median plasma PRL, GH, LH, and CORT are given in Table 1. Ergot drug treatment produced a tenfold decrease in circulating PRL relative to the levels of oil-treated dams. While not differing from each other, Groups ERGO and BROMO exhibited significantly lower plasma PRL levels than that of Group OIL (Mann-Whitney U, $U(1)\leq 36.0$, $p<0.05$). In contrast to the suppressive effect on PRL secretion, the administration of ergot drugs did not significantly alter circulating levels of GH, LH, or CORT.

None of the ergot-treated dams were scored as having lactated on any postpartum day while the oil-treated animals were scored as exhibiting lactation beginning on Postpartum Day 5 and each day thereafter. Analysis of pup body weight change further supported the above observation in that only the pups of Group OIL dams gained weight during the treatment period. An ANOVA test conducted on the body weight change data revealed significant effects due to Drug, $F(2,33)=101.3$, $p<0.001$, Postpartum Day, $F(7,231)=32.6$, $p<0.001$, and Drug × Day, $F(14,231)=30.8$, $p<0.001$.

Our findings clearly show that both ergocornine and bromocriptine produce marked reductions in circulating prolactin (PRL) without influencing plasma levels of growth hormone (GH), luteinizing hormone (LH), and corticosterone (CORT). The fact that PRL is reduced by ergot administration is in concert with a number of previous reports showing that these dopamine (DA) agonists suppress the secretion of this hormone during lactation (e.g., [18]. That ergot drugs are capable of selectively suppressing plasma PRL without influencing circulating GH is supported by earlier work in virgin rats and parturient mice [20,30]. Our results showing unaltered LH levels in postpartum mice are in agreement with other reports showing that ergot treatment does not alter LH secretion in cycling ewes [15], lactating rats [9], and normal human subjects [25]. However, they are at variance with other work demonstrating that ergots are capable of suppressing LH release in cycling [29] and ovariectomized rats [17]. Finally, although afferent pathways for the suckling-induced release of PRL share some of the neural substrates involved in adrenocorticotropin (ACTH) release [24], our findings show that ergot drugs do not alter plasma concentrations of CORT during lactation.

Importantly, our findings also show that ergot-induced reductions in plasma PRL are not related to inadequate suckling stimulation from young. In contrast to previous research in which dams were left with their own young for the duration of ergot drug administration (e.g., [1,27]), postpartum mice in the present study were provided with recently suckled, replete foster young on a daily basis. Because this procedural modification prevented the decline in suckling stimulation that normally occurs in undernourished pups of ergot-treated dams, our findings cannot be attributed to a nonspecific effect of the drug on the viability of young. Our findings add to the growing body of literature suggesting that ergot drugs stimulate pituitary-hypothalamic DA systems and cause a relatively specific suppression of PRL release in postpartum rodents.

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