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Dopamine Inhibits Growth Hormone and Prolactin Secretion in the Human Newborn

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ABSTRACT. **Dopamine is frequently used in neonatal intensive care for its vasopressor, renal vasodilating, and cardiac inotropic properties. The effect of i.v. dopamine infusion on neonatal pituitary hormone secretion is currently unknown. We observed strikingly low serum concentrations of growth hormone (GH) and prolactin (PRL) during a therapeutic, standardized, isovolumetric, partial exchange transfusion (blood sampling every 20 min for 6 h) in two polycythemic neonates requiring intensive therapy, including continuous dopamine infusion. In addition, the secretion of GH and PRL was studied in three neonates with symptomatic polycythemia (gestational age 34–38 wk; birth weight 2110–2530 g; postnatal age 10–30 h) during a partial exchange transfusion, including an intervening dopamine infusion (8 μg/kg/min i.v. for 2 h). The GH and PRL profiles were evaluated by deconvolution analysis. Initially, the three newborns exhibited high-amplitude, pulsatile GH secretion and continuously elevated PRL release. During the dopamine infusion, GH secretion was virtually abolished and PRL release was reduced by at least 50%. Dopamine withdrawal was associated with a rebound release of GH and PRL. Finally, serum GH and PRL concentrations were studied in nine nonpolycythemic newborns (gestational age 31–40 wk; birth weight 1680–4000 g; postnatal age 2–28 d) at the end of a prolonged dopamine infusion (3–5 μg/kg/min i.v. for 2–27 d). Within 2 h after dopamine withdrawal, GH and PRL levels increased a median 3-fold and 10-fold respectively. These data concord to indicate that dopamine is a potent inhibitor of GH and PRL secretion in the human newborn. (*Pediatr Res* 34: 642–645, 1993)**

Abbreviations

GH, growth hormone
PRL, prolactin

Intravenous infusion of the catecholamine dopamine is recommended as the treatment of choice for cardiovascular support of the newborn. As a result, dopamine administration has become common practice in neonatal intensive care. However, dopamine is also a widely distributed neurotransmitter and, in addition, may act as a hormone on the hypothalamic-pituitary axis. At present, the effect of exogenous dopamine on the secretory dynamics of the neonatal anterior pituitary gland have not been evaluated.

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Circulating levels of GH and prolactin PRL have long been known to be strikingly elevated in the newborn (1–3). Recently, deconvolution analysis of GH and PRL profiles revealed that the neonatal hypersomatotropism is characterized by high-amplitude and high-frequency pulsatile secretion of GH without a prolonged GH half-life, whereas hyperprolactinemia appears to be due to GH-independent, continuous PRL release (4).

Here, we provide evidence suggesting that dopamine is a potent inhibitor of neonatal GH and PRL hypersecretion.

SUBJECTS AND METHODS

This report consists of two parts, one with GH and PRL profiles obtained in polycythemic newborns and one with paired GH and PRL evaluations in nonpolycythemic neonates. The serum GH and PRL profiles were obtained in a total of seven newborns. These infants were admitted because of premature birth, low birth weight, suboptimal cardiovascular condition, and/or respiratory distress. All infants were polycythemic, the median venous hematocrit being 0.7 (range 0.65–0.73). The decision to perform a therapeutic partial exchange transfusion was made in each case by the attending neonatologist. Arterial blood samples were obtained every 20 min for 6 h during a standardized, isovolumetric, partial exchange transfusion, as previously described (5).

The serum concentrations of GH were measured by RIA, using a polyclonal antibody (6); the intraassay coefficient of variation was 5.8% at 35 μg/L. The serum concentrations of PRL were measured by immunoradiometric assay using the PRL-IRMA kit (Medgenix, Fleurus, Belgium), having an intraassay coefficient of variation of 6.4% at 27 μg/L. All samples of each infant were assessed in the same assay run.

The sequential GH and PRL concentrations of each infant were evaluated by multiple-parameter deconvolution analysis, a technique examining the possibility of pulsatile hormone secretion, taking into account both the secretory episodes and the metabolic clearance of the investigated hormone (7).

The profile part of this report consists of two sets of studies. First, the GH and PRL profiles from two newborns receiving intensive care including positive pressure ventilation and dopamine infusion (8 μg/kg/min) were analyzed in comparison with the profiles of two newborns not requiring intensive care. The latter infants were matched for gestational age, birth weight, postnatal age, hematocrit (<3% difference), and gender (male).

In the second set of studies, GH and PRL profiles were obtained during a therapeutic partial exchange transfusion in three newborns with symptomatic polycythemia (gestational age 34–38 wk; birth weight 2110–2530 g; postnatal age 10–30 h; hematocrit 0.67–0.73). These infants received additional dopamine support (8 μg/kg/min for 2 h, dissolved in 1 mL of isotonic saline) halfway through the partial exchange transfusion, in accord with the clinical protocol that was used in our neonatal

intensive care unit at the time of these studies. During the partial exchange transfusion, all infants remained euglycemic and had a normal percutaneous oxygen saturation. During the intervening dopamine infusion, the heart rate was increased maximally by 20% compared with the heart rate before and after dopamine administration.

The second part of this report concerns nine nonpolycythemic newborns (gestational age 31–40 wk; birth weight 1680–4000 g; postnatal age 2–28 d) who had been admitted either for intensive care after cardiovascular surgery ($n = 5$) or because of respiratory distress related to prematurity ($n = 4$). These infants had been receiving a prolonged dopamine infusion (median duration 3 d, range 2–27 d; dose 3–5 μg/kg/min at least for 24 h before withdrawal). GH and PRL concentrations were measured in serum obtained through an arterial catheter immediately before and 100–120 min after dopamine withdrawal.

Statistical comparisons were made by Mann-Whitney U test. Approval for these studies and for the use of blood that would otherwise have been discarded was granted by the Ethical Committee of the Medical School, University of Leuven.

RESULTS

The two examined newborns receiving intensive care, including continuous dopamine infusion, were found to have dramatically decreased levels of GH and PRL compared with their matched controls (Fig. 1). Deconvolution analysis of these profiles indicated that the pulsatile secretion of GH in the intensive care patients was decreased in burst amplitude but not in burst frequency or burst duration (4). The PRL secretion rates in the preterm and term infant receiving intensive care were calculated to be respectively one third and one tenth that in the controls.

In the three newborns receiving an intervening dopamine infusion, the latter was accompanied by a striking decrease in the serum concentrations of GH and PRL, whereas dopamine withdrawal was associated with a rapid normalization or transient overshoot of GH and PRL levels (Fig. 2). Deconvolution analysis of these three GH and PRL profiles revealed that the secretion of GH was virtually abolished during the dopamine infusion and was reestablished after dopamine withdrawal (Fig. 3). The secretion of PRL was calculated to be decreased by 50% or more during the dopamine infusion and to be reinstated soon thereafter.

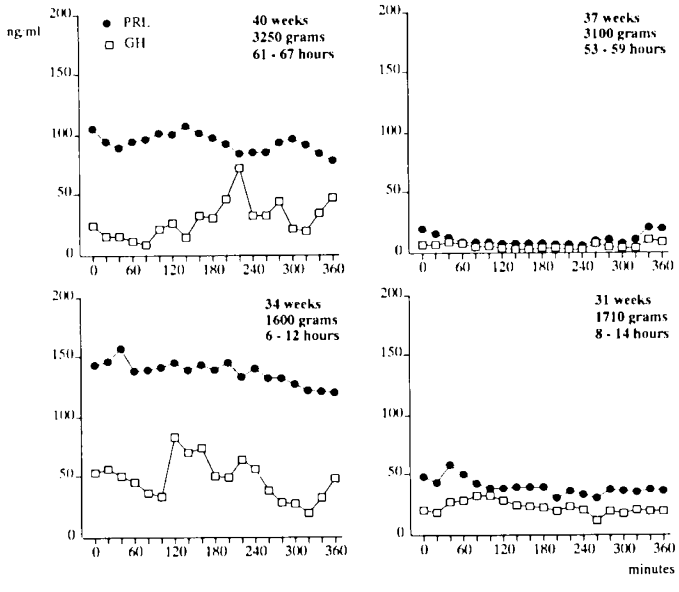

Fig. 1. Serum GH and PRL concentration profiles from two term (*top panels*) and two preterm (*lower panels*) male newborns with polycythemia during an isovolumetric partial exchange transfusion. The low and flattened profiles (*right panels*) are from infants receiving intensive care including dopamine infusion; the profiles in the *left panels* are from control infants, matched for gestational age (wk), birth weight (g), and postnatal age (h). SI conversion: ng/mL = μg/L.

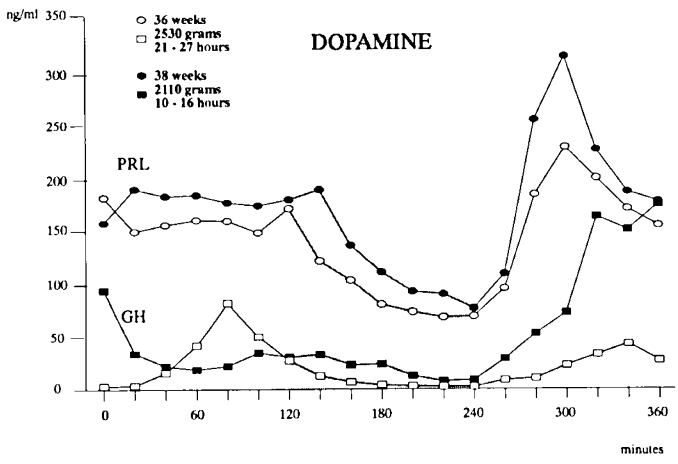

Fig. 2. Serum GH and PRL concentration profiles from two newborns with polycythemia during an isovolumetric partial exchange transfusion and an intermittent dopamine infusion (*shaded area*). The gestational age (wk), birth weight (g), and postnatal age (h) are indicated. SI conversion: ng/mL = μg/L.

In the nine newborns studied at the end of a prolonged dopamine infusion, serum GH concentrations rose ($p = 0.02$) from a median 6 μg/L (range 5–19 μg/L) to 17 μg/L (range 9–53 μg/L) within 2 h after dopamine withdrawal, whereas PRL levels increased ($p = 0.002$) from a median 5 μg/L (range <3–39 μg/L) to 54 μg/L (range 12–134 μg/L).

DISCUSSION

Strikingly low serum concentrations of GH and PRL were found in newborns receiving intensive care, including continuous dopamine infusion. Perinatal stress conditions are usually associated with excessively elevated GH and PRL levels (8, 9). Therefore, the intensive treatment rather than the clinical condition itself was thought to induce the low GH and PRL levels found in these infants. The GH and PRL results from the three infants receiving an intervening dopamine infusion and from the nine infants at withdrawal of prolonged dopamine administration uniformly point toward dopamine as one of the causative factors within the intensive care setting. Together, these observations provide direct and consistent evidence suggesting that dopamine is a potent inhibitor of neonatal GH and PRL hypersecretion.

Our results support the concept that functional dopamine receptors are present in the hypothalamo-pituitary axes governing GH and PRL secretion in the human newborn. Although the concentration of dopamine in the human fetal hypothalamus exceeds that in the adult (10), our data suggest that the dopamine receptors linked to the somatotropic or lactotropic axis are not maximally activated by endogenous dopamine secretion. It is plausible that the infused dopamine exerts its principal action on GH and PRL release directly at the pituitary level. Dopamine has been demonstrated to inhibit pituitary GH and PRL release in *vitro*, through specific membrane-bound dopamine receptors of the D2 subtype (11). Moreover, human newborns receiving dopamine exhibit a blunted PRL response to exogenous thyrotropin releasing hormone (C. Vanhole, F. de Zegher, H. Devlieger, *et al.*, unpublished observations).

It is noteworthy that the inhibitory responses of the newborn presenting with physiologic hypersecretion of GH and PRL parallel the inhibitory responses of GH and PRL to dopaminergic agents in acromegalic adults with pathologic hypersomatotropism and hyperprolactinemia (12). However, our findings regarding suppression of neonatal GH secretion by dopamine contrast

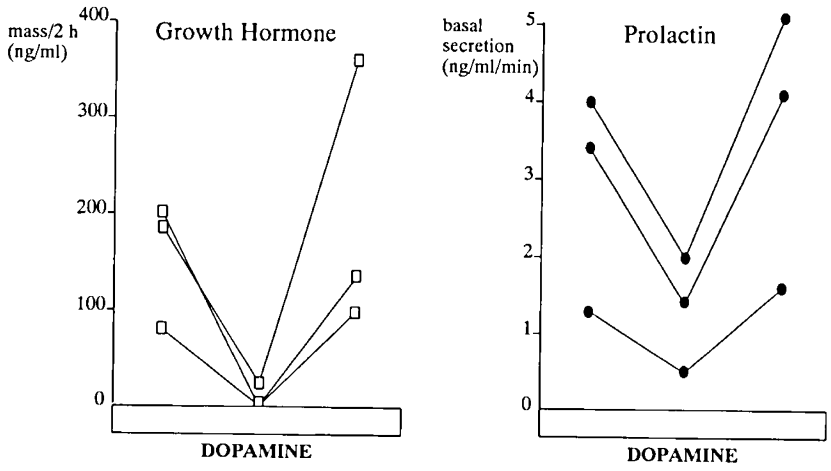

Fig. 3. Results of deconvolution analysis of GH and PRL secretion by three newborns with polycythemia during a 6-h isovolumetric partial exchange transfusion and an intermittent dopamine infusion of 2 h. The amount of pulsatile GH secretion (*left panel*) and the secretory rate of PRL (*right panel*) before, during, and after the dopamine infusion are indicated. The results of each infant are interconnected. SI conversion: ng/mL = μg/L.

sharply with the stimulatory GH response to levodopa and/or dopamine in healthy children and adults (13, 14). These discrepancies in neuroregulation may be related to multiple factors, including age-dependent differences in the number and efficacy of pituitary dopamine receptors and in the regulation of hypothalamic somatostatin secretion and action (11, 14, 15).

The withdrawal of exogenous dopamine was found to evoke a brisk rebound increase in the secretion of GH and PRL. This finding suggests that the dissociation of dopamine from its receptor can function as a signal for GH and PRL release in the human newborn (16). This principle may have a clinical application. The endocrinologic exploration of GH deficiency in infancy is a technically difficult and frequently hazardous enterprise involving multiple blood sampling during, for example, insulin-induced hypoglycemia or a glucagon stimulation test (17). In view of our data, the potential of a "dopamine-withdrawal test" deserves further investigation as a novel alternative in the evaluation of infantile GH secretion.

The decreased secretion of GH and PRL induced by dopamine in newborns may be of clinical significance. GH is an important regulator of intermediary metabolism and a potent growth stimulator at least from birth onward (8, 18). Low plasma PRL concentrations in preterm infants have been associated with a poor outcome, possibly through effects of PRL on surfactant synthesis, whole body water regulation, and gastrointestinal maturation (19, 20). In critically ill adults, the dopamine-induced hypoprolactinemia appears to be associated with a transient decrease of T-lymphocyte proliferative response (21).

In contrast to the brain, where multiple dopamine receptor subtypes exist, the anterior pituitary expresses exclusively dopamine receptors of the D2 subtype, which are present not only on somatotrophs and lactotrophs, but also on thyrotrophs and gonadotrophs (11, 22). Because activation of dopamine D2 receptors results predominantly in inhibitory responses, dopamine emerges as a potential suppressor of the secretion of multiple anterior pituitary hormones (11). In this study, we documented the effect of dopamine on neonatal GH and PRL secretion only. The extent of anterior hypopituitarism induced by dopamine in the newborn remains to be further delineated.

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