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Short Communication

Neonatal glucocorticoid overexposure programs pituitary-adrenal function in ponies

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ABSTRACT

The present study tested the hypothesis that overexposure to endogenous glucocorticoids in neonatal life alters the reactivity of the hypothalamic-pituitary-adrenal (HPA) axis in ponies at 1 and 2 yr of age. Newborn foals received saline (0.9% NaCl, n = 8, control) or long-acting adrenocorticotropic hormone ($ACTH_{1-24}$) (Depot Synacthen 0.125 mg intramuscularly twice daily, n = 9) for 5 d after birth to raise cortisol concentrations 5- to 6-fold. At 1 and 2 yr of age, HPA axis function was assessed by bolus administration of short-acting $ACTH_{1-24}$ (1 µg/kg intravenous) and insulin (0.5 U/kg intravenous) to induce hypoglycemic on separate days. Arterial blood samples were taken at 5 to 30-min intervals before and after drug administration to measure plasma ACTH and/or cortisol concentrations. There were no differences in the basal plasma ACTH or cortisol concentrations or in the cortisol response to exogenous $ACTH_{1-24}$ with neonatal treatment or age. At 1 and 2 yr of age, the increment in plasma ACTH but not cortisol at 60 min in response to insulin-induced hypoglycemia was greater in ponies treated neonatally with ACTH than saline ($P < 0.05$). Neonatal cortisol overexposure induced by neonatal ACTH treatment, therefore, alters functioning of the HPA axis in adult ponies.

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1. Introduction

Glucocorticoids, such as cortisol, increase in concentration toward the end of pregnancy and are essential for tissue maturation in preparation for birth in all species studied to date, including the horse [1]. However, in several species, excess prenatal exposure to these hormones, particularly to synthetic glucocorticoids, has been linked to abnormal functioning of several tissues and organ systems in the adult offspring including the hypothalamic-pituitary-adrenal (HPA) axis [1]. More recently, studies in newborn rat pups have shown that cardiac-, metabolic-, and neuro-development are altered by administration of glucocorticoids shortly after birth [2–4]. The neonatal period may, therefore, be another critical window for glucocorticoid programming, particularly in altricial species that are relatively undeveloped at birth.

In horses, the HPA axis matures late in gestation and is relatively immature at birth compared with other precocious species [5]. Indeed, the major perinatal increment in cortisol occurs immediately after not before birth of the foal and ontogenetic changes in HPA axis function continue after birth in normal healthy animals [5,6]. Horses may, therefore, be more susceptible to glucocorticoid

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programming during the neonatal rather than the fetal period of development. Neonatal cortisol overexposure induced by adrenocorticotropic hormone (ACTH) administration to healthy foals has been shown to alter pancreatic β-cell function up to 13 wk later but had little apparent effect on HPA axis function at 13 wk of age [7,8]. However, its effects on the HPA may not become evident until much later in life in long-lived species [9,10]. Thus, the present study tested the hypothesis that exposure to excess endogenous glucocorticoids during neonatal life alters HPA axis function in ponies at 1 and 2 yr of age.

2. Methods

2.1. Animals and operative procedures

All procedures were carried out under the UK Animal (Scientific Procedures) Act 1986. Seventeen ponies born spontaneously at full term (approximately 325–330 d) were used. After birth (1 d) foals were weighed and received either saline (0.9% NaCl, n = 8, 4 females and 4 males) or long acting ACTH (Depot Synacthen; Alliance Pharmaceuticals Ltd, Wiltshire, UK; 0.125 mg intramuscularly twice daily, n = 9, 5 females and 4 males) for 5 d to maintain an endogenous raise in cortisol concentrations [7]. Plasma cortisol concentrations were determined daily in jugular venous blood samples (4 mL). The foals were housed individually with their mothers and suckled ad libitum. After weaning (5–6 mo), ponies were housed in groups and fed hay (ad libitum) and concentrates (500 g twice per d at 8 AM and 5 PM; Dodson & Horrell, Northampton, UK and H &C Beart Ltd, Brighton Mill, Kings Lynn, UK). At the end of experiments, older than 2 yr, the ponies were either placed with new owners (n = 8) or euthanized (n = 9, 2–3 mg/kg ketamine hydrochloride; Ketaset; Pfizer, Sandwich, UK and 200 mg/kg sodium pentobarbitone; Pentaject, Animalcare Ltd, York, UK) to provide tissue for histologic analyses (saline treated, 3 females and 2 males; ACTH treated, 2 of each sex).

Yearling ponies were premedicated with acepromazine (0.03 mg/kg Novartis Animal Health, Surrey, UK) and detomidine (0.015 mg/kg, Pfizer Animal Health, Sandwich, UK) and then anesthetized with a bolus dose of ketamine (2 mg/kg; Fort Dodge Animal Health Ltd, Southampton, UK) followed by a continuous intravenous (i.v.) infusion of ketamine (20–40 μg/kg/min) and propofol (0.13–0.20 mg/kg/min; Rapinovet; Welwyn Garden City, UK) [11]. After anesthesia, catheters were inserted into the dorsal aorta and inferior vena cava via the superficial circumflex iliac artery and vein, respectively and exteriorized through the flank [12]. This approach allows minimal handling of the animal during an experimental protocol and improves long-term catheter patency relative to catheter placement in the neck. However, a long-term catheter (16 g, central venous catheter, Arrow International Inc, Reading, PA) with sampling extension tube (Tset; Mila International Inc, Florence, KY) was also inserted into a jugular vein for antibiotic administrations and to provide for the possibility of needing to give large volumes of fluid quickly. Antibiotic was given at surgery and for 3 d thereafter (1 g ampicillin i.v., Penbritin, Beecham Animal Health, Brentford, UK). Normal feeding patterns were generally resumed within 24 to 36 h after surgery but no experiments were carried out until at least 7 d after surgery. At the end of experiments as yearlings, the catheters were removed to allow re-catheterization contralaterally ∼1 yr later.

2.2. Insulin-induced hypoglycaemic challenge

To minimize activation of the HPA axis by stress, all experiments were performed in the presence of a second familiar pony and by investigators that had handled the animals regularly since birth. All challenges were started between 9 AM and 10 AM. Hypoglycemia was induced by a bolus dose of insulin (Actrapid human insulin, Novo Nordisk; 0.5 U/kg i.v.) known to induce prolonged hypoglycemia in young foals [13] Arterial blood samples (4 mL) were taken at 5 to 15-min intervals for 30 min before and 60 min after insulin administration (0 min) for measurement of plasma glucose, ACTH, and cortisol concentrations. Blood samples were centrifuged immediately at 3,000 *g* and 4°C for 5 min and the plasma was stored at −20°C. Plasma glucose concentrations were monitored during the 60-min experiment and at 15 to 30-min intervals for 2 h thereafter using an automated analyzer (Yellow Springs 2300 Stat Plus Glucose/Lactate Analyzer; YSI Ltd, Farnborough, UK; coefficient of variation (CV) ≤ 5%, minimum detectable concentration 0.2 mmol/L). At the end of the experiment basal glucose concentrations were restored by glucose infusion (50 mL, i.v., 40% dextrose; Arnolds, Shropshire, UK).

2.3. ACTH challenge

Adrenocortical ACTH sensitivity was assessed by giving short-acting $ACTH_{1\text{-}24}$ (Synacthen; Alliance Pharmaceuticals Ltd; 1 μg/kg body weight, i.v.) as a bolus dose flushed in with saline [14]. Arterial blood samples (4 mL) were taken at 5 to 30-min intervals for 30 min before and 120 min after ACTH administration (0 min) for measurement of plasma cortisol concentrations. The hypoglycemic and ACTH challenges were given in a random order separated by at least 3 d.

2.4. Biochemical analyses and adrenal histology

Plasma cortisol concentrations were determined using a commercial assay kit (Coat-A-Count Cortisol; Siemens Medical Solutions Diagnostics, Los Angeles, CA) validated for equine plasma [7]. The sensitivity of this assay was 0.04 ng/mL. The intra-assay CV was 2.0% and the inter-assay CV was 5.0%. Plasma ACTH was measured using a commercial double antibody ^{125}I RIA kit (Diasorin, Stillwater, MN) validated for use with equine plasma [5]. The lower limit of detection for the assay was 10 to 25 pg/mL. The intra-assay CV was 3.6%, and the inter-assay CV was 8.4%. The left adrenal was fixed in 4% (wt/vol) phosphate-buffered paraformaldehyde, dehydrated and embedded in parafin wax before 4 sections (5 μm) were cut transversely through its midline. The sections were stained with hematoxylin and eosin, and the thickness of the total and 3

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