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Original Research

Long-term Treatment of Insulin-insensitive Mares with Cabergoline: Effects on Prolactin and Melanocyte Stimulating Hormone Responses to Sulpiride and on Indices of Insulin Sensitivity

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ABSTRACT

The main experiment assessed whether the inhibitory effects of the dopamine agonist, cabergoline, on prolactin and α-melanocyte stimulating hormone (MSH) concentrations would persist throughout a longer-term administration (65 days). The possible effect of cabergoline on insulin sensitivity was also studied. Ten mares known to be insulin insensitive were allotted to two groups (treated vs. control). An insulin challenge, a glucose tolerance test, and a sulpiride challenge were administered before treatment. On day 0, treated mares (n = 5) received an injection of 5 mg cabergoline in slow-release vehicle; control mares (n = 5) received an equivalent vehicle injection. Injections were repeated every 10 days for a total of seven injections. Sulpiride challenges were done 1 day before each cabergoline treatment to assess possible refractoriness to the treatment. Behavior and hair coat density were also monitored. Plasma prolactin was suppressed ($P < .01$) to undetectable levels in mares receiving cabergoline; control mares had robust prolactin responses to each sulpiride injection. There was no indication of refractoriness to cabergoline over time. Plasma MSH concentrations after sulpiride were also suppressed ($P < .05$) by cabergoline. After treatment, neither the glucose response to insulin nor the insulin response to glucose differed ($P > .1$) between groups. No behavioral changes were noted because of treatment. Weight of hair samples indicated that cabergoline perturbed ($P < .05$) winter coat growth. It is concluded that 5 mg of cabergoline in slow-release vehicle administered every 10 days is an effective way of delivering dopaminergic activity to mares that results in no noticeable detrimental effects and no refractoriness to the drug.

1. Introduction

Recent research by Hebert et al [1] indicated that the long-acting dopamine agonist, cabergoline, in a slow-release formulation suppressed plasma prolactin secretion in mares for at least 10 days after a single intramuscular injection. Moreover, the suppression was complete, even in the face of low-dose sulpiride challenges [1], which, in the absence of cabergoline, caused relatively consistent elevations in prolactin secretion in both mares

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and estrogen-treated geldings [1,2]. Similarly, injections of pergolide in slow-release vehicle suppressed prolactin secretion, but for a much shorter period of time [1]. Because only one injection of cabergoline was tested in the experiment of Hebert et al [1], the possibility of long-term detrimental effects or refractoriness could not be assessed.

Hebert et al [1] suggested that the dopaminergic effects of cabergoline observed for prolactin secretion would likely be similar for melanotrope hormonal output, primarily α-melanocyte stimulating hormone (MSH) and perhaps adrenocorticotropin in pituitary pars intermedia dysfunction (PPID), because of the similar physiologic control by dopamine (via the portal blood for lactotropes and via neural input for melanotropes [3,4]). Hebert et al [1] did not include plasma MSH concentrations in their report, thus we are providing those data herein as a prelude to the main experiment. Recently, we have reported that mares displaying hyperleptinemia, hyperinsulinemia, and a diminished response to injected insulin also have exaggerated MSH responses to sulpiride and thyrotropin releasing hormone [5], similar to, but not as great a magnitude of, horses displaying symptoms of PPID [6,7]. Currently, horses and ponies diagnosed with PPID are treated with pergolide mesylate, a dopamine agonist known by its trade name Prascend. Although it has been reported to have good success rate, the medication needs to be fed daily for the duration of the horse's life [8].

The present (main) experiment was designed primarily to test the long-term effects of repeated cabergoline injections (every 10 days for a total of seven injections) on prolactin and MSH concentrations. Insulin-insensitive mares were monitored for any overt detrimental effects to cabergoline injection (e.g., behavioral changes), for any sign of refractoriness to cabergoline, and for any changes in hair coat that might be predicted from previous reports in which inadvertent immunization of pony mares against prolactin in the winter-delayed hair shedding, later in the spring [9]. In addition, given the similarity in MSH response to secretagogue [5] between the insulin-insensitive horses, first described by Gentry et al [10] and subsequently characterized by Cartmill et al [11] and Caltabilota et al [12], and horses either displaying or testing positive for PPID, we also evaluated whether cabergoline injections would improve the insulin sensitivity (i.e., increase the glucose response to insulin or reduce the insulin response to glucose infusion) in these insulin-insensitive mares as part of our ongoing study of their characteristics.

2. Materials and Methods

Procedures used in these experiments were approved by the Institutional Animal Care and Use Committee of the Louisiana State University Agricultural Center.

2.1. Preliminary Experiment

2.1.1. Mares and Treatments

Selected plasma samples collected from two groups (of three) in the experiment of Hebert et al [1] were used to assess the effect of a single 5-mg injection of cabergoline on the MSH response to a low dose of sulpiride administered 10 days after cabergoline injection. Briefly, 10 mares ranging in age between 5- and 16-year-old, weighing between 480 and 616 kg, with body condition scores [13] between five and eight were used. On October 21, 2011 (day 0), five of the mares received a single intramuscular injection of cabergoline (Attix Pharmaceuticals, Toronto, ON, Canada) in 1.0 mL of a proprietary mixture of hydrophobic, oily liquids designed to slow down and produce a sustained release of drug over time. Five other mares received an equivalent injection of vehicle at the same time and served as controls.

Small doses of sulpiride (2 μg/kg of body weight [BW] of the racemic mixture; Sigma Chemical Co, St. Louis, MO) were administered to each mare via intravenous injection in saline on days −2, −1, 0, 1, 2, 3, 4, 6, 8, and 10 relative to cabergoline or vehicle injections. Jugular blood samples were collected from each mare immediately before and at 10, 20, 40, and 60 minutes after sulpiride injection. Heparinized plasma was harvested and subsequently stored at −15°C.

2.1.2. Sample and Data Analyses

Plasma from the day −1 and day 10 sulpiride challenges was selected for measurement of MSH with commercially available kit reagents (Euria α-MSH RIA; Immuno-Biological Laboratories, Minneapolis, MN). Estimates of the limit of detection (concentration of hormone equivalent to the mean number of counts per minute of the assay zero standard tubes minus two standard deviations of those counts from the mean) of the assay and the intra-assay coefficient of variation were 1.4 pmol/L and 6.6% for the single MSH assay.

Data for MSH concentrations were analyzed by analysis of variance (ANOVA) using the general linear model of SAS (SAS Institute, Cary, NC). They were analyzed as a double-split-plot design, with treatment as the main effect, repetitive challenges (day −1 and 10) as the first repetition, and multiple sampling times within each challenge as the second split. Treatment was tested with the mare within treatment term, and each subsequent split was tested with the appropriate interaction of mare within treatment for that split. Differences between groups within time periods were assessed by the least significant difference test [14].

2.2. Main Experiment

2.2.1. Mares and Treatments

Ten light horse mares between the ages of 11 and 22 years, weighing between 486 and 584 kg, and with body condition scores [13] of six to eight were selected from the resident herd because of their continual testing as insulin insensitive, based on the technique described by Caltabilota et al [12], more than at least three different trials; the latest assessment was completed in early August, 2011. Such mares are also hyperleptinemic and hyperinsulinemic and display an exaggerated MSH response to sulpiride and thyrotropin releasing hormone stimulation [5]. All mares were housed on pasture consisting of primarily alicia bermudagrass intermixed with common bermudagrass, bahiagrass and Dallis grass, and white clover. Hay prepared in summer from the same pasture grasses