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Progesterone Metabolism by the Liver and Brain During the Estrous Cycle of Heifers

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Progesterone in blood varies because of amount of progesterone secreted from the corpus luteum and amount metabolized. Results indicate the primary site of progesterone metabolism is the liver.

Summary

Heifers were used to evaluate progesterone metabolism in the liver and brain during the estrous cycle. Blood samples were collected from the carotid artery and jugular, portal and hepatic veins. Progesterone concentrations in the hepatic vein were less than in portal and jugular veins and the carotid artery, but there were no differences between the carotid artery and jugular and portal veins. Progesterone concentrations in the hepatic, portal and jugular veins represented 25, 89 and 86 percent of concentrations in the carotid artery, respectively. During the estrous cycle much of the progesterone in blood is metabolized by the liver.

Introduction

The amount of any hormone in circulation is regulated by the rate of hormone release from the endocrine gland and the rate of hormone degradation in the organs that metabolize it. The liver is a major site of hormone metabolism and it contributes to the maintenance of peripheral concentrations by degrading most hormones during a single passage. Metabolic function in the liver also involves processing and degradation of steroids that are produced in the body or administered via injections or implants. In some species, organs other than the liver also contribute to progesterone metabolism. In sheep, for example, progesterone metabolism by the brain accounts for a significant amount of total progesterone clearance. There are no reports of the uptake of progesterone by the liver, portal drained viscera or the brain in cattle. Therefore, the objective of this study was to quantify amounts of progesterone metabolized by the liver and brain of heifers, and to assess differences in amounts of progesterone metabolized during different days of the luteal phase of the estrous cycle.

Procedure

Six postpubertal heifers of composite breeding (1/4 Hereford, 1/4 Angus, 1/4 Red Poll, 1/4 Pinzgauer; 716 $\pm$ 44 lb of body weight) were surgically fitted with permanent indwelling catheters in the hepatic vein, two mesenteric veins and portal vein. Heifers were allowed to recover from surgery for one month before initiation of sampling periods. During surgery, the right carotid artery was isolated and placed subcutaneously. The carotid artery, along with the jugular vein, were catheterized one day before each period of sample collection. Estrus was synchronized in all heifers with two injections of prostaglandin $F_{2\alpha}$ given 11 days apart.

Blood samples were taken simultaneously from the hepatic, portal and jugular veins and from the carotid artery at 30 minute intervals for three hours, on days seven, 11 and 15 of the estrous cycle subsequent to synchronization. To determine blood flow on the day of sample collection, heifers were continuously infused through the mesenteric vein with a solution of 2 percent (w/v) of para-amino hippuric acid (PAH). To quantify concentrations of PAH in circulation, 5 mL of blood was simultaneously withdrawn from hepatic and portal veins and the carotid artery every 30 minutes for three hours. Concentrations of progesterone in plasma were analyzed by radioimmunoassay.

Results

Mean concentrations of progesterone in circulation in the carotid artery, jugular, hepatic and portal veins of heifers consistently increased with day of the estrous cycle ($P<.01$). No differences were found ($P>.10$) among mean concentrations of progesterone from the jugular and portal veins and carotid arteries of all heifers pooled over all days (Table 1). This indicates the amount of progesterone metabolized by neither the brain nor the portal drained viscera is significant. Mean concentration of progesterone in the jugular vein during the luteal phase of the estrous cycle of all heifers represented 77 to 92 percent, with an overall average of 86 percent of the concentration in arterial blood.

Table 1. Least squares means of circulating progesterone concentrations in different blood vessels of heifers, pooled over three days during the luteal phase of the estrous cycle (ng/mL)[a]

	Blood vessel			
Heifer	Carotid	Jugular	Portal	Hepatic
1	6.9	5.9 (85.3)	6.4 (92.8)	0 . 9 [b] (12.8)[13.9]
2	7.7	5.8 (76.6)	6.9 (89.2)	1 . 0 [b] (12.9)[14.5]
4	6.9	5.9 (92.2)	5.9 (91.2)	0 . 9 [b] (13.8)[13.6]
6	8.8	7.6 (86.1)	7.2 (82.1)	0.5[b] (5.2)[6.4]
Mean	7.5[d]	6.3 (84.2)[d]	6.8 (91.3)[d]	0 . 8 [e] (11.3)[12.1]
3	7.2	6.5 (90.3)	6.6 (92.2)	4 . 0 [c] (55.0)[59.7]
5	7.5	6.8 (90.6)	6.8 (90.0)	4 . 1 [c] (55.1)[61.2]

Table 2. Blood flow (BF) through the portal and hepatic veins (L/h), net flux of progesterone (P_4) through portal drained viscera (PDV), hepatic tissue and total splanchnic flux (TSF), and net uptake of progesterone during the mid-luteal phase of heifers[abcd]

	Blood Flow (L/h, $\bar{x} \pm$ SE)		Net flux of progesterone (ng/h, $\bar{x} \pm$ SE)			
Day of the estrous cycle	Portal	Hepatic	PDV	Hepatic	TSF	P_4 uptake (mg/h)
11	400[e] ± 16	460[e] ± 20	-298 ± 38	-1877 ± 183	-2174 ± 154	2.17 ± 0.15
15	296[f] ± 6	368[f] ± 8	-156 ± 49	-2092 ± 179	-2248 ± 211	2.24 ± 0.21

[a]Blood flow = Infusion rate of PAH/[Venous PAH (mg/L) - Arterial PAH (mg/L)] x 0.06. Infusion rate of PAH = 4000 mg/h.
[b]PDV = (Portal P_4 - Arterial P_4) x PBF.
[c]Hepatic Flux = (Hepatic P_4 - Arterial P_4 x ABF) + (Hepatic P_4 - Portal P_4 x PBF). Arterial Blood Flow (ABF) = HBF - PBF.
[d]TSF = PDV flux + Hepatic Flux.
[ef]Values in the same column with different superscript differ (P<.05).

The latter value indicates the amount of progesterone metabolized by the brain is only 14 percent. Mean concentration of progesterone in portal blood was equivalent to 89 percent of the concentrations of progesterone in the carotid artery (range 82 to 93 percent), indicating that progesterone metabolism by portal drained viscera is about 11 percent. In this study, circulating concentrations of progesterone in the hepatic vein of four heifers were about 12 percent of that present in portal circulation. The latter value means the efficiency of progesterone metabolism by the liver is about 88 percent, indicating most splanchnic degradation of progesterone in these four heifers was carried out by the liver.

Mean concentration of progesterone in the hepatic vein was significantly less (P<.01) compared with the carotid artery (Table 1). Concentrations of progesterone in the hepatic vein indicate approximately 75 percent of total progesterone is metabolized by the liver and portal drained viscera together. Differences were found in mean concentrations of progesterone in the hepatic vein among heifers. Mean concentrations of progesterone in the hepatic vein were significantly less (P<.01) than in portal and jugular veins and the carotid artery in four of six heifers during days seven, 11 and 15 of the estrous cycle. In two of six heifers, concentrations of progesterone in the hepatic vein were significantly greater (P<.01) than in the other four heifers during the three sampling periods.

Findings from this study could help explain individual differences in response to treatments with progesterone to synchronize stage of estrous cycles in cattle because some animals are capable of degrading more progesterone than others. Differences in metabolism rate of progesterone by the liver and portal drained viscera among heifers would allow for differences in the amount of negative feedback of progesterone on gonadotropin secretion and response to progesterone-based treatments to synchronize estrous cycles of cattle.

Estimated values of blood flow through the liver on day seven of the estrous cycle could not be calculated because of problems incurred with infusion of PAH, and hence data were discarded from analyses involving blood flow. Blood flow through the liver was greater (P<.05) on day 11 than day 15 of the estrous cycle (Table 2); this difference could not be explained physiologically. No differences (P>.10) were detected in blood flow through the liver among heifers within days of the estrous cycle. No differences (P>.10) were found between days 11 and 15 of the estrous cycle in net flux of progesterone in the portal drained viscera, in the net flux of progesterone through hepatic tissue and in the net uptake of progesterone by the liver.

In summary, total progesterone metabolism by the brain and by the portal drained viscera of heifers was not significant. The primary site of metabolism was the liver with up to 88 percent of progesterone that entered this organ being metabolized. Another important finding: there were individual differences among heifers in amount of progesterone metabolized by the liver.

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