Effect of Hamster Pregnancy on Female Protein, a Homolog of Serum Amyloid P Component (44420)

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Abstract. **Pentraxins such as human serum amyloid P component (SAP) and C reactive protein (CRP) represent an ancient family of proteins that are ubiquitous in nature and have evolved with little change in structure or regulation. The pentraxin in the Syrian hamster (*Mesocricetus auratus*) is unique because it is preferentially expressed in the female at high constitutive levels and accordingly called female protein (FP) or FP(SAP) due to its close homology with human SAP. The high levels of FP in female serum (100-fold greater than male serum) suggested its role in hamster pregnancy, one of the shortest of any eutherian mammal. We determined the serum FP concentration in pregnant Syrian hamsters and found a marked decrease (>80%) at term with the nadir at parturition with subsequent increase. A similar downregulation of FP was found in the normal female Syrian hamster after injury (acute phase response), so in both cases the assumed beneficial effects were achieved with less, rather than more pentraxin, a paradoxical pentraxin response. The fall in serum FP concentration could represent a response to protect the fetus from the high and potentially toxic level of FP normally found in the female, that is harmful because of its association with amyloidosis. An FP that is 97.5% identical to Syrian hamster FP is found in the Turkish hamster (*Mesocricetus brandti*), although serum levels in females are much lower, and amyloid is very rare. During pregnancy/parturition of Turkish hamsters, the serum level of FP remained remarkably constant. In a more distantly related hamster, the Armenian hamster (*Cricetulus migratorius*), serum FP actually increased during pregnancy and at parturition in a manner similar to that found in the Armenian hamster during an acute phase response. The heterogeneity of FP kinetics during pregnancy in these three species of hamster indicates pleomorphic gene structure for regulation of their similar FPs, and suggests that this protein may have a different function in the pregnancy of each species.** [P.S.E.B.M. 1999, Vol 221]

Pentraxins represent an ancient family of proteins widely expressed in nature, from horseshoe crab to man, and their structure has changed little during a long evolution (1). Two main types of pentraxin, called serum amyloid P component (SAP) and C reactive protein (CRP), are found in human serum. In addition to having a common sequence and configuration (a cyclic pentamer of five noncovalently assembled monomer subunits), pentraxins also share common characteristic properties, such as binding to polysaccharide ligands and nuclear constituents, and interacting with leukocytes and complement components (2). Furthermore, their synthesis in hepatocytes is usually regulated in a similar way, such as increased production after tissue injury in a process called an acute phase response (3). This prompt and vigorous increase of circulating pentraxin after tissue damage has promoted the idea that these proteins represent a primitive defense system that functions to protect and restore the compromised host. The pentraxin found in the Syrian hamster is more homologous with human SAP (4) with a 73% identical amino acid sequence (5), but because of its preferential expression in

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females, it was called female protein (FP) or FP(SAP) (6). In light of the preserved structure, predictable behavior, and similar expression of pentraxins, the regulation of FP(SAP) synthesis in the Syrian hamster is quite remarkable because of the unique role that sex hormones play in regulating its production in the liver. In this species, males normally have low serum levels of FP (0.01 mg/ml) and the usual upregulation of FP synthesis in an acute phase response, similar to the pentraxin expression in other mammals (7). In contrast, the FP level in normal females is more than 100-fold greater (1.0–2.0 mg/ml), and it actually decreases during an acute phase response (7), suggesting that lower serum FP levels are advantageous in the injured female hamster. FP(SAP) is a constituent of hamster amyloid (8), and the unusually high serum concentration of FP in the normal female Syrian hamster is directly associated with the early deposition of amyloid in the aging animal (9). This results in a shortened life span in the female when compared with the male, an unusual occurrence in mammals (10). The conservative evolution and ubiquitous expression of pentraxins implies an important function for these proteins; however, their main purpose remains obscure. The extensive sex hormone control of FP(SAP) synthesis in the Syrian hamster suggests that this protein may have a role in reproduction, for example, during pregnancy.

In this report, the effect of pregnancy and parturition on the synthesis of FP in the Syrian hamster was studied. In addition, we examined Turkish hamsters and Armenian hamsters during pregnancy because these hamsters express closely related homologous FPs that are also under sex hormone control, albeit not identical with that found in the Syrian hamster (11, 12).

Materials and Methods

Animals. Syrian hamsters (*Mesocricetus auratus*), Turkish hamsters (*Mesocricetus brandti*), and Armenian hamsters (*Cricetulus migratorius*) were obtained from the Rocky Mountain Laboratories animal production unit. They were fed Purina lab chow, given water *ad libitum*, and maintained in rooms lighted only artificially (14 hr light/10 hr dark per 24 hr for Syrian and Armenian hamsters and 16 hr light/8 hr dark for Turkish hamsters).

Drugs. Progesterone (Sigma Chemical, St. Louis, MO) at a final concentration of 40 mg/ml, was incorporated into a solution of sesame oil containing 10% benzyl benzoate. Prostaglandin F2′ (Lutalyse) was obtained from Upjohn Co. (Kalamazoo, MI), and 0.5 mg injected subcutaneously (SC) twice daily for 5 days. Ibuprofen (5 mg in PBS/ethanol) and indomethacin (2 mg in PBS/ethanol) from Sigma were injected twice daily. Dr. Dave Sherwood (U. of Illinois, Champaign, IL) generously supplied relaxin, and 0.2 mg was injected SC three times per day for 4 days into nonpregnant female Syrian hamsters.

Experimental Design. Individually caged female hamsters were bred by male hamsters placed with them at random (Armenian hamsters) or during the evening of the third day of estrus as determined by vaginal discharge (Syrian and Turkish hamsters). Under Aerrane (Anaquest) anesthesia, they were bled (0.025–0.050 ml) from the retroorbital plexus at various intervals during pregnancy, parturition, and postpartum. The concentration of FP in serum was determined as before by ring diffusion analysis using a rabbit antibody species specific for the particular FP being measured; that is, anti-Syrian hamster FP for Syrian hamster (6), anti-Turkish hamster FP for Turkish hamster (12), and anti-Armenian hamster FP for Armenian hamster (11). 0.1 *M* EDTA was routinely incorporated into the agarose to preclude any interaction between it and FP (11). The preparation/use of I^{125} labeled FP and calculation of T 1/2 were done as previously described (8).

Data were analyzed using the *T*-test for significant difference.

Animal experiments were conducted in accordance with NIH guidelines for animal care and use.

Results

Figure 1 shows the average serum concentration of FP during the gestation period of 12 primiparous Syrian hamsters (2–3 months of age) compared with control nonpregnant females. It is apparent that a significant decrease occurs during pregnancy/parturition. From Day 8 to Day 16, the FP concentration declined 86%, from an average value of 1.72 to 0.25 mg/ml and then promptly increased after delivery. Figure 2 shows the individual concentration curve of four primiparous females closely monitored at the time of par-

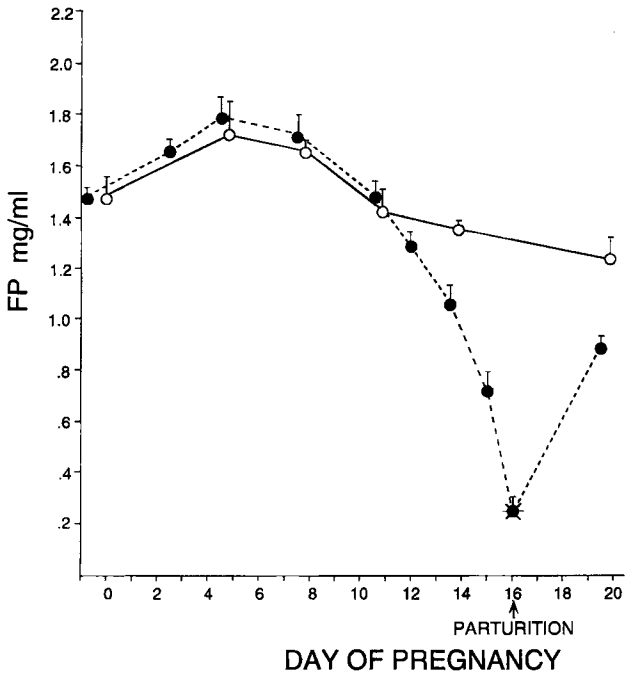

Figure 1. Serum FP change during pregnancy of primiparous Syrian hamsters (●) (n = 12), compared with control normal, nonpregnant female hamsters (○) (n = 6). Serum FP concentration declined >80% during parturition. Data points represent the mean values, bar = 1 + SEM.

turition. Frequent plasma samples taken on Days 15, 16, and 17 show that the FP level decreased to a low of 0.1 mg/ml and that the nadir of FP concentration occurred at parturition, with rapid recovery to normal levels afterward. An especially prompt recovery occurred in the female that lost her litter shortly after delivery (Fig. 2). The change in FP concentration was also examined during pregnancy-parturition of three older multiparous female hamsters 6–7 months of age, and similar FP changes were found. One of these is shown in Figure 2, because this female was sick after delivery, killed her pups on Day 18, and died on Day 21. The progressively lower serum concentration of FP seen in this female before death has been observed in other female hamsters dying from various causes (7, 13).

FP(SAP) could be consumed in the female during various pregnancy-associated changes. To determine if the decrease in serum FP level during pregnancy was due to increased catabolism of FP, I^{125} FP was injected intravenously (IV) into four female hamsters on the 14^{th} day of pregnancy (about 44 hr before delivery). The half-life (T 1/2) of serum I^{125} FP was determined from serial plasma samples obtained during the next 3 days. The T 1/2 of I^{125} FP was identical with that found in four normal nonpregnant females (T 1/2 = 25 hr) which were incorporated as controls, indicating that the low serum FP levels in gravid females were a result of downregulation of hepatic synthesis (data not shown). In addition, a similar FP T 1/2 was obtained when four females were tested within 4 hr of delivery.

As in other mammals, a decrease in the serum level of progesterone in the Syrian hamster is associated with termination of pregnancy, and these falling progesterone levels during the last 2 days of pregnancy may be important in triggering parturition because injections of progesterone at that time will delay onset of delivery (14). To determine the effects of a delayed parturition on serum FP levels, progesterone (4 mg/day) was injected beginning on Day 8 of pregnancy (Fig. 3). This regimen interrupted not only parturition

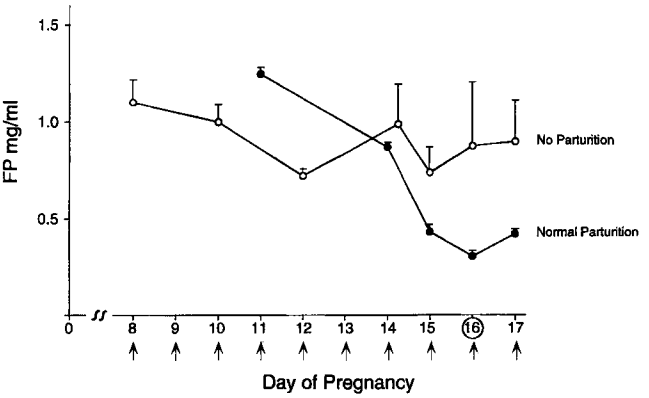

Figure 3. Serum FP in pregnant Syrian hamsters with (○, $n = 3$) or without (●, $N = 4$) injections of progesterone (4 mg) daily starting on Day 8 of pregnancy. Progesterone injection delayed parturition and also abrogated the FP decline during the terminal portion of pregnancy. Data points represent mean value, bar = + 1 SEM.

that was expected on Day 16, but also the normal downregulation of FP during the last 4 days of pregnancy.

Relaxin is another hormone involved in parturition, but when injected into three nonpregnant female Syrian hamsters, the concentration of FP in serial plasma samples did not change. Prostaglandin synthesis increases during labor and a number of studies have indicated its importance in parturition (15). Yet, when prostaglandin $F_2\alpha$ was given to five nonpregnant females, no change in serum levels of FP was detected.

To test for an acute phase response causing lower serum FP levels during pregnancy/parturition, indomethacin, a nonsteroidal anti-inflammatory agent that is also a potent inhibitor of prostaglandin synthesis, was given to three hamsters from Day 8 of pregnancy to term. This treatment had no detectable effect on the serum FP levels or parturition of the pregnant animals. Another nonsteroidal anti-inflammatory agent, ibuprofen, also was given to three hamsters during the last 8 days of pregnancy without any detectable effect on serum FP or parturition (not shown).

The factor(s) responsible for turning off hepatic syn-

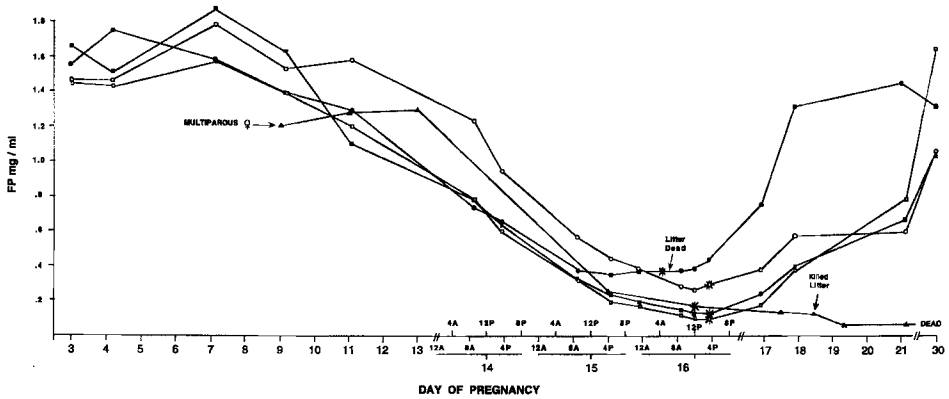

Figure 2. Individual serum FP levels of four primiparous females closely monitored around parturition, showing lowest levels achieved around time of delivery (*). Normal levels promptly returned after delivery, especially in one female after the death of her litter. Serum FP during pregnancy of three multiparous females was similar, and one of these was shown (multiparous). This particular female died 5 days postpartum, and her FP levels progressively declined before death.

thesis of FP during the terminal phase of pregnancy is presumably present in serum. However, we were unable to detect downregulation of serum FP when three normal female hamsters were injected (IV and IP) with serum (6 ml) obtained from pregnant female hamsters (not shown). Also, placental suspension and amniotic fluid from parturient hamsters were injected (IP and IV) into two normal female hamsters without detectable effect on the concentration of FP in serum (not shown).

Perhaps the unusually high pentraxin concentration found in serum of female Syrian hamsters is toxic for the developing fetus or young suckling pup, and the downregulation of FP synthesis represents an adaptation necessary for a successful pregnancy. To test for FP toxicity at parturition, we passively transferred whole serum from normal female hamsters to three terminally pregnant hamsters in an attempt to increase their serum concentration of FP at this critical time. Use of whole serum was inefficacious, as IP injection of 5 ml (x2) on Day 14 and 5 ml (x3) on Day 15 produced only a minimal (10%) elevation of serum FP in the parturient hamster, and no alteration of parturition or viability of pups at birth (not shown).

Serum FP During Pregnancy in the Turkish Hamster. The Turkish hamster is a close relative of the Syrian hamster and has a very similar serum FP although serum FP levels in normal females are much lower (10-fold) than those found in the female Syrian hamster (12). Kinetics of serum FP during the 15-day pregnancy (16) of the Turkish hamster were much different from those of the Syrian hamster (Fig. 4), as FP remained remarkably constant without a significant change during pregnancy in the Turkish hamster, with a modest decrease during parturition.

FP During Pregnancy in the Armenian Hamster. Serum of the Armenian hamster also contains an FP homologous to that of the Syrian hamster, but the Armenian species is more distantly related to the Syrian and Turkish hamsters, and there are many differences in FP regulation (11). An entirely different pattern of change was apparent during pregnancy in this hamster (Fig. 5) because serum FP transiently increased about 4-fold on Day 13 with a smaller 2-fold increase during parturition on Day 18.

Discussion

Sex hormones are known to regulate synthesis of secreted proteins that are critical to the reproductive process. For example, circulating female specific proteins necessary for egg production/maturation have been described in insects (17, 18) and in blood of laying chickens (19); many pregnancy associated proteins have been defined in the blood of mammals (20). Syrian hamster FP(SAP) is another serum protein regulated by sex hormones and preferentially expressed in females. However, its importance to the female and to reproduction is unknown. Furthermore, FP is a pentraxin, and although these proteins are found in most animals, sex hormones are rarely involved in controlling pentraxin synthesis. Indeed, pentraxins are well known for their antiquity and a conservative evolution with little change in their structure or regulation. It is not known why hepatic synthesis of FP(SAP) became regulated by sex hormones during the evolution of hamsters or why unusually high levels are found in the female Syrian hamster. Nevertheless, it is reasonable to speculate that this unique sex-limited expression of a pentraxin protein in the Syrian hamster may in some way be related to female reproduction. Hamsters are also noteworthy because they have the shortest gestation period of any eutherian mammal (14). It is possible that the normally high levels of FP in the female Syrian hamster, which are associated with formation of amyloid (8, 9), may have a toxic effect on the developing conceptus (fetus or placenta) or suckling pup, so that downregulation actually evolved as a mechanism to protect the fetus at term or while nursing. Previous studies showed no evidence for the passage of pentameric serum FP(SAP) through the placenta or through colostrum (6). However, serum levels were low during this period of observation and fetal-neonatal transfer would therefore be difficult to detect. In the present report, we were unable to passively increase serum FP enough to

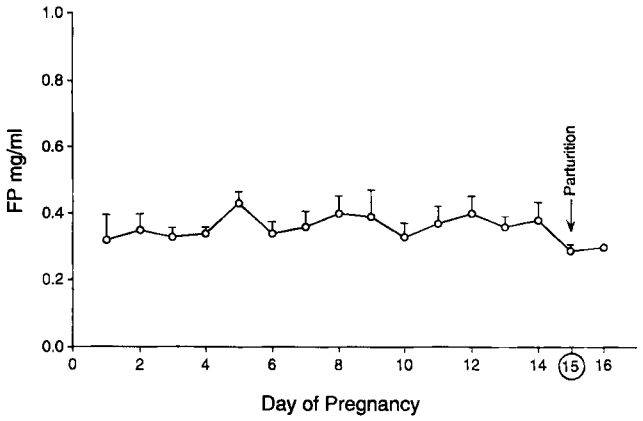

Figure 4. Changes in serum FP concentration in five pregnant Turkish hamsters. When compared with Syrian hamsters, FP concentration is normally lower in serum of Turkish hamsters, and no significant changes were detected during pregnancy or parturition. Data points represent mean value, bar = + 1 SEM.

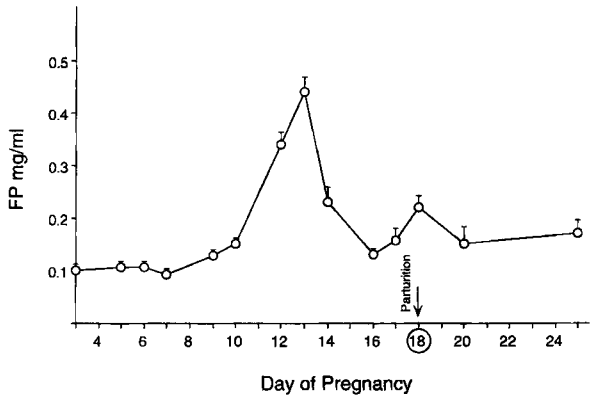

Figure 5. Serum FP level during pregnancy of five Armenian hamsters. FP levels are normally around 0.1 mg/ml and increase on Day 13 of pregnancy and again at time of delivery on Day 18. Data points represent mean value, bar = + 1 SEM.

test for its toxicity at term, but this is a feasible experiment if a sufficient quantity of purified FP becomes available.

The mechanism responsible for downregulation of FP synthesis by the liver during late pregnancy/parturition of Syrian hamsters also is unknown. Decreased serum FP levels in female Syrian hamsters have been observed in three other situations: 1) after administration of testosterone, which downregulates (x100) the normal female serum levels of FP(1–2 mg/ml) to normal male levels (0.010 mg/ml) (6); 2) during an acute phase response, 36–48 hr after injury, FP levels in females transiently decrease to about 50% of normal levels; this negative acute phase response is caused primarily by circulating cytokines that downregulate hepatic synthesis (Ref. 7; Coe J, unpublished data); and 3) FP levels decrease in females destined to die, and these very low FP levels are a harbinger of death and can accurately predict impending death from a variety of maladies (7, 13). One hamster that died postpartum (Fig. 2) showed this continued fall of FP concentration before death. The mechanism responsible for this extreme antemortem downregulation of FP synthesis is unknown, but it is not due to a generalized hepatic failure.

Progesterone is important in maintaining pregnancy in mammals, and falling serum levels are associated with parturition in the Syrian hamster (14). In the present study, injections of progesterone prevented parturition as previously shown (14), and without parturition the FP levels did not fall. This result indicated that downregulation of FP synthesis is not programmed during early pregnancy, but depends upon an intact progression of hormonal changes during pregnancy. Decreasing levels of progesterone cannot alone explain the onset of FP downregulation because FP levels normally start to drop on Day 10–12 of pregnancy, a time when progesterone levels are still rising at a rapid pace and only after Day 14 do they abruptly fall to the very low levels at parturition (14). Furthermore, we have been unable to show a change in serum levels of FP after the administration of progesterone to normal female hamsters (Coe J, unpublished data). Identification of the mechanism responsible for the downregulation of this pentraxin during pregnancy is indeed difficult because a multifactorial process is probably involved, and the pregnant hamster tolerates only limited experimental manipulations. Nevertheless, nonpregnant female hamsters were tested with some of the factors, such as relaxin and prostaglandin, which should be present at parturition. However, the absence of any effect by these factors in nonpregnant females does not rule out a completely different response to these same factors in the pregnant female. Similarly, the circulating factors in pregnant serum responsible for turning off hepatic synthesis of FP may be effective only in the hormonal background of the pregnant animal and therefore are undetectable when tested by passive transfusion into a nonpregnant female. The profound downregulation of FP achieved at parturition is remarkably similar to that found in dying females observed in previous experiments (7, 13), although it seems unlikely that impending death and normal pregnancy/parturition would trigger a common mechanism for turning off FP synthesis.

Syrian and Turkish hamsters, both in the genus Mesocricetus, are very close cousins. They share very short gestation periods and also a sex hormone controlled FP that is 97.5% identical at the amino terminus (12). However, as reviewed in Table I, regulation of FP in the female Turkish hamster is different from female Syrian hamsters in at least three ways (12). In normal Turkish hamster females, 1) the acute phase response results in upregulation of FP synthesis; 2) a circannual control is evident with higher summer serum levels; and perhaps most importantly, 3) the serum levels are about 10-fold lower, and amyloid is essentially nonexistent in this species. The lower FP levels in Turkish hamster females may be responsible for the paucity of amyloidosis and may also represent a nontoxic level to the developing fetus so that the serum concentration of FP does not need to decrease during pregnancy in the Turkish hamster. Note that at parturition, female Syrian and Turkish hamsters shared a similar serum FP level.

The Armenian hamster, in a different genus (Cricetulus), is more distantly related to the other two Mesocricetus hamsters. Its FP is less similar (85% identical) (21), and its sex hormone control is different (11) (Table I). Indeed, estrogen administration downregulates FP synthesis (11) and can even initiate hepatic tumors (22, 23). Also, this hamster has a longer gestation (18 days) (24) during which serum FP actually increases, similar to the upregulation in its acute phase response (11). A modest increase in serum levels of

Table I. Expression of Female Protein

Hamster species	Chromosome no.	FP identity, %	Serum levels, mg/ml		Seasonal variation, ♀	Acute phase		Testosterone control	Estrogen control	Pregnancy/ parturition	High levels with amyloid	Low levels with death	Reference
			♀	♂		♀	♂						
Syrian, *Mesocricetus auratus*	44	100	1.0–2.0	0.001–0.01	0	↓	↑	Yes↓	No	↓↓↓	Yes	Yes	4, 5, 6, 7, 8, 9
Turkish, *Mesocricetus brandti*	44	97.5	0.1–0.5	0.001–0.01	↓Winter	↑	↑	Yes↓	No	0	No	No	12
Armenian, *Cricetulus migratorius*	22	85	0.1–0.2	0.1–0.2	↑Winter	↑	↑	No	Yes↓	↑	No	No	11

pentraxin have been observed in mice during delivery (SAP) (25) and in women in labor (CRP) (26, 27). CRP is the acute phase pentraxin in humans. It has been studied extensively in serum of pregnant women with the general conclusion that its levels change little during pregnancy and can increase modestly during normal labor with further elevations indicative of an infectious complication (28). It is notable that changes of FP serum level in pregnant Syrian and Armenian hamsters reflect their respective downregulation and upregulation responses as seen during the acute phase response. The Turkish hamster is the exception, as the substantial upregulation of FP normally seen after injury (12) was not seen during pregnancy or parturition.

We are not aware of studies that have looked for the presence of SAP in placental tissue. However, SAP proteins are known to be a constituent of glomerular basement membrane (29) and are associated with microfibrils in various connective tissues (30–32). The present study has been restricted to observations on circulating FP in blood. However, intravascular FP is in a very dynamic equilibrium with extravascular FP (8). The intracellular dynamics of pentraxin physiology are unknown, but the reversible dissociation of this oligomer into its hydrophobic ≈ 27-kDa monomer subunits (33), provides a fascinating mechanism for it to penetrate many otherwise hostile cellular compartments.

In the extensive search for pentraxin functions, research has focused on looking for the beneficial effects from pentraxins because they characteristically are upregulated in an acute phase response, suggesting that higher serum levels of pentraxin are advantageous to the injured animal and speed repair of damaged tissue. The unusual downregulation of FP(SAP) in the female Syrian hamster during an acute phase response suggests the opposite relationship; that is, the inflammatory response is somehow enhanced by less serum FP(SAP). Similarly, the downregulation of FP during late pregnancy may present another situation where lower pentraxin levels are beneficial to the mother or fetus or both.

The definition of a critical pentraxin function in humans has eluded investigators for more than 50 years, and the role of FP(SAP) in hamster physiology and pregnancy also remains obscure. Indeed, the heterogeneity of FP serum kinetics during pregnancy in these three hamsters would suggest that FP is fulfilling different function(s) in each species. Assuming a similar hormonal milieu during pregnancy in the three hamster species, the different FP responses would indicate that the response elements controlling these three similar FP genes were subject to extensive modification and variation. Hamster FP provides an interesting example of evolution being dominated by changes in the regulation of its synthesis rather than changes in its structure.

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