Placenta Ingestion Enhances Opiate Analgesia in Rats

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KRISTAL, M. B., A. C. THOMPSON AND H. L. GRISHKAT. *Placenta ingestion enhances opiate analgesia in rats.* PHYSIOL BEHAV 35(4) 481–486, 1985.—Analgesia, produced by either a morphine injection or footshock, was monitored (using a tail-flick test) in nonpregnant female rats. Analgesia was induced within minutes of having the rats eat one of several substances. When the substance eaten was rat placenta, both the morphine- and shock-induced types of analgesia were significantly greater than in controls that ingested other substances (or nothing). When footshock (hind-paw) was administered in conjunction with the opiate antagonist naltrexone, the analgesia produced was attenuated but detectable; in this case, placenta ingestion did not enhance the analgesia, suggesting that the effect of placenta is specific to opiate-mediated analgesia. Placenta ingestion, in the absence of an analgesia-producing manipulation, did not elevate pain threshold. It is possible that this enhancement of analgesia is one of the principal benefits to mammalian mothers of ingesting the placenta and birth fluids (placentophagia) at delivery.

Opiates   Placenta   Parturition   Analgesia   Naltrexone   Footshock   Placentophagia
Pregnancy   Afterbirth   Pain   Maternal behavior   Tail-flick test   FSIA

THE norm during parturition in placental mammals is for the mother to consume the placenta and associated fluids and membranes (placentophagia) as they are are delivered, or soon afterward. There has been a good deal of research and speculation regarding the benefits to the mother, or indirectly to the infant, of engaging in this behavior [14, 16, 31] but until now, no answer has been forthcoming. In the laboratory rat, placentophagia appears not to be necessary for the performance of adequate maternal behavior, nor is it critical for the onset of the postpartum estrus or (except for one obscure report [23]) for lactation [4, 18, 22]. Kristal has hypothesized that there may be immunological benefits of placentophagia to the mother or, through the milk, to the offspring [14], but this hypothesis has not been tested. Finally, other explanations, even if they were true for some species, might not be applicable to the majority. For example, if placentophagia were to reduce the possibility of attracting predators to the nest, this function would not apply for nonnesting species. It is not reasonable to assume that it is a vestigial behavior in some species, and although there may be multiple overlapping advantages, it is not parsimonious to assume that the behavior has entirely different benefits to different taxonomic groups.

Though conflicts in findings have not yet been resolved, much current research in humans and rats indicates that CNS and plasma levels of endogenous opiates increase during pregnancy and peak at or around parturition [5, 7, 10, 13, 19, 20, 25, 26]. In the rat, pain threshold also rises during pregnancy and peaks at or around delivery, and the administration of the opiate antagonist naltrexone blocks this "pregnancy-induced analgesia" [9]. Interestingly, the high plasma level of endorphin seen at delivery is not high enough to produce analgesia in a nonpregnant individual [8]. Since placentophagia occurs at the period of maximum analgesia in parturient rats, we investigated the possibility that this behavior affected the pain threshold of rats.

We used nonpregnant rats to study the effect so that the influence of placenta ingestion would not be confounded by the previous presence of the placenta within the body of the female, by the rapid changes in hormone levels, by the sensory effects of uterine distention and contraction, or by the effects on pregnancy and delivery of testing pain threshold.

EXPERIMENT 1

The first experiment was designed to examine the effect of placenta ingestion on pain threshold in nonpregnant rats that had received an injection of either morphine sulfate or saline vehicle.

Our preliminary work suggested the possibility that placenta ingestion enhanced morphine-induced analgesia, but did not itself produce analgesia. In that study we used a 5 mg/kg dose of morphine sulfate, which produced the maximum elevation (8-sec ceiling) of tail-flick latency in all subjects. Therefore, the only dimension of analgesia we could observe to change, because of the ceiling effect, was duration. Each rat received an injection of morphine or vehicle, followed by a 20-min exposure to an ingestible substance, followed immediately by a tail-flick test. Tests were repeated at 20-min intervals for the next 2 hr. Those rats that were fed control substances or nothing showed a return to normal tail-flick latency by 80 min after the ingestion period; those that ate placenta did not return to baseline tail-flick latency during the 100-min post-ingestion test period. The control groups showed latencies that were significantly shorter than those of the placenta-eating group by 20 min

after ingestion. Placenta ingestion prolonged the analgesia, but because of the ceiling effect we could not determine whether it had also heightened the analgesia. We decided, therefore, to use a threshold dose of morphine sulfate, 3 mg/kg, in the first experiment, so that increases in the level of analgesia could be detected.

METHOD

Subjects

Sixty-four Long-Evans virgin female rats, approximately 120 days old, were used. The rats were housed in 24.5×18×18-cm hanging, galvanized, wire-mesh cages, in a colony maintained on a 14 hr on/10 hr off daylight cycle. Testing was conducted during the first five hours of the day phase. Except during testing, the rats could feed (Agway Prolab Rat/Mouse/Hamster Formula 3000) and drink ad lib. Only rats willing to eat placenta were used. Since relatively few virgin Long-Evans rats spontaneously eat placenta, all the subjects for this study were induced to eat placenta for the first time by food deprivation [14,15]. Each rat was repeatedly exposed to placenta (or a control substance) until she reliably ate 3–4 g of it within a 20-min presentation period.

Apparatus

The measurement we chose for assessing pain thresholds was the standard "tail-flick" algesiometer used in many laboratories [1,3]. The dependent variable was the number of seconds it took for the tail of the rat to move out of the stimulus field (a spinal reflex) after the onset of a continuously-applied beam of intense light. Movement of the tail terminated the beam. Our tail-flick apparatus was similar to the prototype described in the literature [3]. A 500 W reflector-type projector bulb delivered light (and therefore heat) through a 1.8-cm aperture in a thin wooden platform. The rat's tail lay across the aperture, and was 2 cm from the bulb. Constant light output was maintained as the bulb aged by monitoring the light with a photo-cell attached to a digital resistance meter, and increasing the input to the bulb with a potentiometer. The beam intensity was adjusted so that it produced a tail flick in 3–4 sec in a normal rat; the trial ended automatically after 8 sec, to eliminate the possibility of tissue damage in subjects experiencing analgesia. Latencies were timed with a digital stopwatch accurate to 0.01 sec. Rats were restrained in an opaque polyvinyl chloride tube (5×21 cm) to which they had been habituated for 1 hr/day for the 5 days preceding the test.

Procedure

The rats were distributed evenly among eight groups: four groups were to eat rat placenta, cookie mash, ground beef, or nothing, 15 min after an injection of morphine sulfate (3 mg/kg, IP), and another four groups received these treatments after an injection of isotonic saline (1 ml/kg, IP). The dose of 3 mg/kg of morphine was chosen because it produced a small but measurable analgesia in about half the pilot subjects. This reduced the possibility of a ceiling effect.

Placenta was obtained surgically from Day-21 pregnant rats killed with CO_2. The placentas were quickly frozen, along with a few drops of physiological saline, at $-20°$ C until needed. For presentation they were warmed rapidly to 37° C, and presented in an untippable glass dish [14]. Ground beef
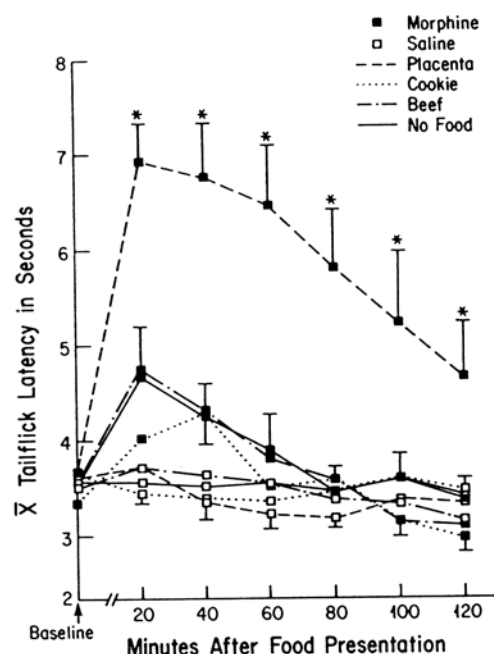

FIG. 1. Mean tail-flick latencies (±SEM) of virgin rats that received either a morphine (threshold dose, 3 mg/kg) or saline injection, then a 20-min exposure to either placenta, cookie mash, ground beef, or an empty dish. The Morphine + Placenta Group, which had the same mean baseline latency as the other groups, showed significantly longer latencies than all other groups on all trials (*$p < < 0.05$).

was used as a control for meat per se. Fresh USDA Choice ground sirloin, obtained locally at a retail market, was stored and presented identically to placenta. To control for ingestion of a highly palatable substance, which placenta apparently is once a rat has been induced to try it [14], two of the groups were presented with a mash of cookies and milk [14, 15, 24]. It consisted of a mixture of 10 ml reconstituted powdered whole milk (Carnation) and a 10 g chocolate chip cookie (Chips Ahoy, Nabisco). The mash was presented the same way as the placenta and beef.

Each subject was food deprived for the 2 hr preceding the test, and were deprived of lab chow and water during the 2-hr test.

During the experiment, the rats were proffered either 8 placentas (about 4.8 g), 5 g cookie mash, or 5 g ground beef. The unfed rats were presented with an empty dish.

Tail-flick latencies were recorded before the injection and 20, 40, 60, 80, 100 and 120 min after the start of the 20-min "food" presentation period (which began 15 min after injection).

A vaginal smear from each rat was obtained and analyzed on the day of testing to determine whether the magnitude of the effects we observed was related to stage of the estrous cycle.

RESULTS

During the 20-min "food" presentation period, the rats ate an average of 3.9±0.4 g placenta, 3.2±0.4 g cookie mash, and 3.7±0.4 g ground beef.

Figure 1 depicts the results of the first study. There were no differences among the groups in baseline tail-flick latency, F(7,56)<1.0. The mean baseline latencies ranged from

3.36±0.09 sec (Cookie + Morphine Group) to 3.68±0.08 sec (Cookie + Saline Group).

The four morphine-injected groups had longer tail-flick latencies (higher pain thresholds) than did their respective saline controls; however, in the cookie-eating and unfed groups the difference was extremely small, and statistically significant only on one of the first two trials (Newman-Keuls, $p<0.05$). On the other hand, the morphine-injected rats that had eaten placenta showed a dramatic elevation of tail-flick latency, which persisted throughout the entire series of trials (120 min). The overall ANOVA showed a significant 3-way interaction (Drug × Food × Trial, $F(18,336)=2.72$, $p<0.002$, with a Greenhouse-Geiser correction). Subsequent tests involved 2-way ANOVAs and pairwise comparisons.

Tests of the Food × Trial interaction yielded significance only in the morphine condition, $F(18,168)=3.61, p<0.001$. A probe of this interaction revealed that the morphine-treated rats that ate placenta had significantly longer latencies, on all trials, than did morphine-treated rats that ate other substances.

A Newman-Keuls test indicated that at 20 min after "food" presentation, the latencies of the Beef + Morphine (mean=4.74±0.47 sec) and No Food + Morphine (mean=4.67±0.46 sec) Groups were significantly longer than that of the Cookie + Morphine Group (mean=4.01±0.26 sec, but as Fig. 1 shows, that difference is minor.

The interaction of Drug × Trial within the placenta condition was significant, $F(6,84)=13.97, p<0.0001$. Among rats that ate placenta, those that received morphine had significantly longer latencies than did their saline-treated controls on all trials.

At 20 min after "food" presentation, the No Food + Morphine Group (mean=4.67±0.46 sec) had significantly longer latencies than the No Food + Saline Group (mean=3.55±0.13 sec), $F(1,14)=5.43, p<0.05$. At the 40-min trial, the Cookie + Morphine Group (mean=4.27±0.30 sec) had significantly longer latencies than the Cookie + Saline Group (mean=3.40±0.13 sec), $F(1,14)=4.78, p<0.05$.

There were no significant correlations between the magnitude of analgesia and stage of the estrous cycle in any groups.

In summary, the results of Experiment 1 show that (a) rats that received morphine (3 mg/kg), but not placenta, showed only a very slight analgesia; (b) those that received both morphine and placenta showed a dramatic elevation and prolongation of analgesia; (c) placenta did not affect pain threshold in rats that did not receive morphine.

DISCUSSION

Although placenta and amniotic fluid do contain opioids [12], ingested placenta, itself, is apparently not an analgesic. Not only did the Placenta + Saline Group show no elevation in tail-flick latency, but we were able to determine from our laboratory records that in morphine-treated females presented with various amounts of placenta, maximum enhancement was achieved when they ate 2 to 4 placentas (1–2 g); as the number increased toward 12 (7–8 g), there was a linear decline in the enhancement effect ($r=-.77, p<0.01$). It is possible that as the amount of placenta eaten (within a 20-min period) increased, the enhancement effect became offset by the lowering of pain threshold that is observed after large meals [17]. Under normal circumstances, although rats often eat more than 12 placentas during a delivery, these become available at a rate of about one every 10 to 40 minutes, not 12 in one 20-min period. An alternative explanation, of course, is that the active ingredient in placenta shows a biphasic response, a low-dose enhancement of analgesia and a high-dose inhibition.

EXPERIMENT 2

We tested whether placenta ingestion would enhance analgesia brought about by means other than the administration of morphine. Electric shock applied to the paws of a rat produces a brief but reliable elevation in pain threshold. Furthermore, there is some evidence that the analgesia produced by front-paw shock and that produced by hind-paw shock are mediated by different mechanisms: analgesia produced by front-paw shock is completely blockable with naloxone, which only partially blocks analgesia produced by hind-paw shock [27,30].

METHOD

Subjects

Thirty-six adult virgin female Long-Evans rats, housed and maintained identically to the rats in Experiment 1, were evenly divided into six groups: Placenta + Front-paw Shock; Placenta + Hind-paw Shock; Placenta + No Shock; Nothing + Front-paw Shock; Nothing + Hind-paw Shock; and Nothing + No Shock.

Apparatus

Footshock-induced analgesia was administered in a standard operant-conditioning chamber with a floor of 0.32-cm steel rods that were positioned 1.4 cm apart. Shock was delivered to the bars by a Grason-Stadler constant-current shock generator/scrambler.

Footshock was confined either to the forepaws or hindpaws by lifting either the pelvis or shoulders of the rat off the floor with a noose of soft nylon string. We adjusted the shock parameters for front-paw and hind-paw delivery, using pilot rats, so that the increase in tail-flick latency was about the same for each. The values we used for front-paw and hind-paw shock were 2.5 mA for 120 and 90 sec, respectively.

The tail-flick testing apparatus was the same as that used for Experiment 1.

Procedure

The procedures for collection, storage, preparation, and presentation of placenta were identical to those used in Experiment 1.

Pain threshold was determined by tail-flick latency using the same equipment and procedures as in Experiment 1.

First, a baseline tail-flick latency was determined (T_b, baseline trial). Then a placenta- (or nothing-) presentation period occurred, which lasted for 20 min. Immediately afterward, tail-flick latency was measured again (T_p, post-ingestion, pre-shock trial). Footshock was then applied, and tail-flick latency was measured each minute for the next 10 min.

RESULTS

The rats in the Placenta groups ate an average of 1.67±0.23 g of placenta.
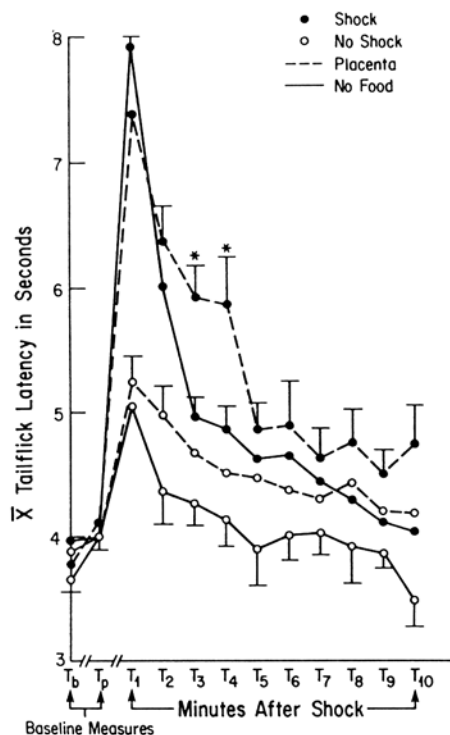
There were no differences between the Front-paw and

FIG. 2. Mean tail-flick latencies (±SEM) of virgin rats at successive 1-min intervals after the induction of analgesia by footshock. T_b is baseline measure before placenta and before footshock. T_p is baseline measure after placenta but before footshock. Data from rats given front-paw shock and hind-paw shock were pooled. The shocked rats receiving placenta showed significantly greater analgesia than did other rats (*$p < 0.05$).

FIG. 3. Mean tail-flick latencies (±SEM) of virgin rats given two injections of naltrexone (5 mg/kg each), in conjunction with hind-paw shock and placenta or hind-paw shock alone. T_b is baseline measure before naltrexone and before placenta. T_1 values were between those obtained previously for shocked rats and unshocked rats: naltrexone attenuated but did not eliminate footshock-induced analgesia. Placenta eaters and unfed rats were not different on any trial.

Hind-paw Shock groups, $F(11,110) < 1.0$. The results from these two groups were therefore combined, and are presented in Fig. 2.

Mean baseline tail-flick latencies for the four groups were not significantly different from one another, $F(3,32) < 1.0$, and ranged from 3.68 ± 0.07 sec (Nothing + No Shock Group) to 3.94 ± 0.11 sec (Nothing + Shock Group).

Both shocked groups showed the same significant elevation in tail-flick latency (and presumably, pain threshold), indicating that analgesia was produced by the footshock, $F(3,32) = 52.01$, $p < 0.0001$. We found that we could not vary the analgesia produced by footshock as subtly as that produced by morphine injection, so that we could not eliminate the ceiling effect. At T_1, most of the shocked rats showed the maximum latency (8 sec). Therefore, it is difficult to determine whether analgesia was heightened or prolonged. The Placenta + Shock rats reliably showed greater analgesia for 2 or 3 min longer than did the rats in the other groups. It should be noted that there was a small but marginally significant difference between the No Food + Shock Group and its control, the No Food + No Shock Group, at T_3 and T_4 (Newman-Keuls, $p = 0.05$), indicating that by this comparison, footshock alone produced a measurable analgesia through the fourth trial. It is clear though, that the latencies of the Placenta + Shock Group at T_3 and T_4 are significantly greater than those of the No Food + Shock
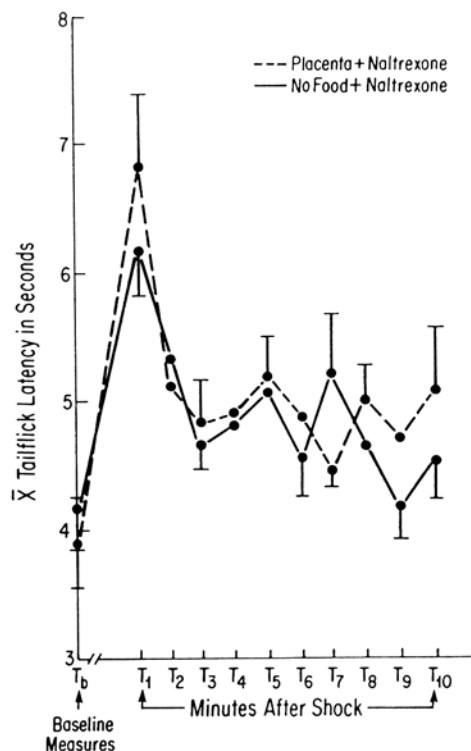
Group, T_3: $F(3,32) = 3.82$, $p < 0.02$; T_4: $F(3,32) = 6.35$, $p < 0.01$; Newman-Keuls, $p < 0.05$.

The unshocked control groups showed a small but significant elevation of tail-flick latency at T_1, $F(1,10) = 157.43$, $p < 0.01$. This may have been due to the stress of being harnessed and partially lifted off the floor of the chamber. However, the latencies of the groups that received shock were clearly, and significantly, higher.

In summary, the results of Experiment 2 show that (a) consonant with reports in the literature, front-paw shock and hind-paw shock both produced a brief but reliable analgesia; (b) placenta ingestion enhanced the analgesia produced by footshock; and (c) no differences between front-paw shock-induced analgesia and hind-paw shock-induced analgesia were detected.

EXPERIMENT 3

According to previous reports, analgesia produced by hind-paw shock is supposed to be mediated, in part, by opiates, since it is partially blockable by administration of opiate antagonists [27]. On the basis of the results of Experiment 2, we could not determine whether placentophagia was having an effect by modifying an opiate system or by modifying an opiate component of a combined opiate and nonopiate system, since its effects on front-paw shock-induced

analgesia and hind-paw shock-induced analgesia were the same.

In the third experiment, therefore, we administered the opiate antagonist naltrexone to rats receiving hind-paw shock. Presumably, naltrexone should eliminate that portion of hind-paw shock-induced analgesia mediated by opiates, leaving a small but detectable amount of analgesia mediated by a nonopiate system. If placenta ingestion has its effect by modifying opiate-mediated analgesia, as the results of Experiment 1 suggest, it should be ineffective in enhancing the analgesia remaining in the naltrexone-treated rats.

METHOD

Subjects

Twelve adult virgin female Long-Evans rats, housed and maintained as in Experiments 1 and 2 , were tested.

Apparatus

The apparatus for administering footshock, and that to test tail-flick latency, were the same as those used in Experiment 2.

Procedure

All 12 rats were tested for baseline tail-flick latency, then received an injection of naltrexone (5 mg/kg, SC). Twenty minutes later, they received a second injection of naltrexone. Six rats were then given a dish containing 3 placentas (apparently the optimal dose, and equal to the amount of placenta eaten by the rats in Experiment 2), and 6 were given an empty dish. Twenty minutes after that, the rats received the same dose of hind-paw shock as the previous groups, and tail-flick latency was again measured.

RESULTS AND DISCUSSION

Figure 3 depicts the tail-flick latencies of the naltrexone-treated rats in Experiment 3.

There were no differences between the baseline tail-flick latencies of the two groups (Placenta + Shock + Naltrexone: mean=3.88±0.12 sec; No Placenta + Shock + Naltrexone: mean=4.14±0.08 sec; $F_{(1,10)} < 1.0$), nor were these different from the baseline latencies of the rats in Experiment 2, $F_{(5,42)} < 1.0$ (see Fig. 2).

All the rats in the Placenta + Naltrexone Group ate all the placenta they were given.

The naltrexone-treated rats showed a measurable, but attenuated and abbreviated footshock-induced analgesia. The T_1 latencies of both groups were significantly elevated above baseline (Newman-Keuls, $p < 0.05$). By the second trial, T_2, tail-flick latencies of the naltrexone-treated rats were no longer significantly different from those of the previous groups that did not receive footshock (see Fig. 2), Newman-Keuls, $p > 0.05$. At T_2, the latencies of the naltrexone-treated rats, whether they received placenta (mean=5.08±0.20 sec) or not (mean=5.39±0.25 sec), had returned to the baseline range, and were significantly shorter than those of previously tested rats receiving shock and placenta(mean=6.38±0.47 sec), (Newman-Keuls, $p < 0.05$). Furthermore, the effect of naltrexone was the same for the placenta-eaters and unfed rats across all trials, $F_{(10,100)} < 1.0$. This indicates that the administration of nal-

trexone eliminated the differences we had observed in Experiment 2 between placenta eaters and unfed rats after footshock (in Fig. 3, at T_2, for instance, the rats fed placenta had a mean latency of 5.08±0.20 sec, and those fed nothing had a mean latency of 5.39±0.25 sec).

The results of Experiment 3 are consistent with reports by others that hind-paw footshock analgesia is mediated only partly by an opiate mechanism, since it can be only partly blocked by an opiate antagonist [27], and suggest further that placentophagia has its effect on footshock-induced analgesia by influencing the opiate-mediated portion of the phenomenon.

GENERAL DISCUSSION

The findings show that the ingestion of placenta dramatically enhances analgesia that results from increased opiate levels in the body. These increased opiate levels can be produced by an injection of morphine or by the application of footshock.

Although we did not test parturient rats, we think that our results suggest that heightened analgesia during and after delivery is a significant benefit of parturitional placentophagia. An obvious experimental strategy in investigating the consequences of parturitional placentophagia would be to prevent primipara from eating placenta as it is delivered. The problem we have encountered repeatedly is that removing placenta as it is delivered is extremely distressing to the mother rat: indeed, it is far easier to remove pups at that time. The mother attacks and bites the fingers or forceps taking the placenta and shows a subsequent disruption of delivery, in that the next pup may be delayed for 30–75 min. If the procedure is repeated with the delivery of the next pup, the delivery process may stop entirely. A second consideration is that amniotic fluid ingestion may produce the same effects as placenta ingestion, and the female begins to have access to amniotic fluid when, or even before, the fetus is expelled.

Our results also suggest that ingested placentas do not contain sufficient amounts of analgesics to affect the mother directly. It is possible that an opiate release is elicited either by the act of placentophagia itself, or by substances present in the placenta. However, this seems unlikely because (a) placenta ingestion seems to have no effect on a system that has not already been primed with opiates, (b) the effect of eating more than 3 or 4 placentas showed an inverse dose response, and (c) too high a level of opiates in the system at delivery can have a deleterious effect on maternal behavior [2, 11, 21]. It is more likely that placenta, and perhaps amniotic fluid, contain or stimulate the release of a substance that potentiates the effect of opiates already in the system (for instance by blocking cholecystokinin [6, 28, 29]). The advantage of an opiate potentiator is clear: more analgesia can be produced by less endogenous opiate.

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