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Review article

Placentophagia and the Tao of POEF

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ABSTRACT

Placentophagia, ingestion of placenta and amniotic fluid, usually during parturition, is a behavioral feature of nearly all nonaquatic, placental mammals, and is a nexus for several interlocking behavioral phenomena. Placentophagia has not been typical of human cultures, but in recent years, some women in affluent societies have engaged in it, thereby bringing publicity to the behavior. First, we summarized benefits of placentophagia for nonhuman mammals, which include increased attractiveness of neonates, enhanced onset of maternal behavior, suppression of pseudopregnancy, and enhancement of opioid hypoalgesia by Placental Opioid-Enhancing Factor (POEF), a benefit that may extend well outside the context of parturition. The research on POEF in animals was discussed in detail. Then we discussed placentophagia (placentophagy) in humans, and whether there is validity to the claims of various benefits reported primarily in the pro-placentophagy literature, and, although human afterbirth shows POEF activity, the POEF effect has not yet been tested in humans. Finally, we discussed the general possible implications, for the management of pain and addiction, of isolating and characterizing POEF.

1. Placentophagia in nonhuman mammals

1.1. Summary and history

Placentophagia, the ingestion of the placenta or amniotic fluid, or both, is a common and somewhat mysterious feature of nonhuman mammalian birth and maternal behavior. At the beginning of the 20th Century, Dr. J.P. O'Leary, a veterinarian at the Bureau of Animal Industry, in Buffalo, New York, wrote a review in the *American Veterinary Review* of a paper by T. Wieland that had appeared in the *Berliner Tierarztliche Wochenschrift* and that had summarized the current thinking about placentophagia and reproductive physiology. Writing initially about rabbits and guinea pigs, O'Leary stated:

> "…They are instinctively compelled to eat their placenta only, and all mammalian females eat their own placental membranes…. And this eager desire, this necessity to devour their placenta is peculiar to all mammalian females, carnivora as well as herbivora, and it is even common among tribes of people in Asia, Africa, and Oceanica, who are even at the present day placentophagists…. The thyroid gland secretes iodine, arsenic and phosphoric bases, which play an important part in the formation of the skin and its appendages, hide, feathers, brain, genital organs, and the embryo. The excess of these substances is excreted in the form of menstruation in those females which have little hair upon the skin, and as long as there is no foetus to consume them…. Now additional organic juices flow together into the placenta and accumulate there for the development of a new being. Everything that the female body can produce, it stores up in the placenta…. This natural instinct [placentophagia] becomes a benefit. It impels the mother to make use of this valuable source of nutrition, which is created from her own body, even if she belongs to a species to which flesh foods are usually abhorrent. Since it has an especial value for her at this moment; it creates a strong desire to eat and digest the afterbirth. Every female which can eat all or a part of her placenta, recovers more quickly from her confinement and the milk secretion makes its appearance more rapidly and more plentifully." (O'Leary, 1906, pp. 590–591).

Nonhuman mammals of almost all taxonomic groups indeed engage in placentophagia; aquatic mammals are a notable exception (Slijper, 1960; Lehrman, 1961; Kristal, 1980; Kristal, 1991; Kleiman et al., 1997; Kristal et al., 2012). Camelids were also considered an exception in the early literature (e.g., Lehrman, 1960), but this assumption was based originally on observations of domesticated camels. Note: Without an

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ethogram with which to compare the behaviors of captive and domesticated animals to those of their wild counterparts, or without a comparison of a variety of species, data from a single species of captive or domesticated animal, to represent an exception, should not be taken at face value (Hediger, 1955; Houpt, 2011; Cesarini and Pulina, 2021). Marsupials resorb the placenta, but certainly ingest amniotic fluid at delivery (for review, see Kristal, 1980). Although normally these tissues are not available to mammals outside the context of parturition and are not necessarily attractive to nulliparae (Kristal and Williams, 1973, 2003), the enthusiasm with which puerperae (mothers with newborn), and even fathers in at least one species of hamster (Gregg and Wynne-Edwards, 2006), consume the afterbirth is surprising. Rat mothers, for instance, react to the removal of pups from the birthing area with less agitation than they react to the removal of placentas (Kristal, 2009). Furthermore, rats and monkeys (both omnivores), have been observed to refuse meats other than placenta at delivery (Tinklepaugh and Hartman, 1930; Kristal, 1973). In regard to the pIacenta itself, it should be noted that omnivores (e.g., rodents and primates, including humans) have a placoid placenta – a solid mass of tissue almost the size of the fetus. Placentas of most carnivores and herbivores are much different; they consist of either large (herbivore) or microscopic (carnivore) islets of placental tissue scattered over the amniotic membrane (Kristal, 1980; Wooding and Burton, 2008). Therefore, it is easier and more probable to observe parturitional placenta-eating in omnivores than in herbivores, and in herbivores more than in carnivores. However, they can all be observed to ingest amniotic fluid by licking the young.

Proximate causality for the avid consumption of afterbirth during delivery in nonhuman mammals, especially herbivores and some omnivores, can almost certainly be attributed to "specific hunger", a relatively simple process that makes certain necessary substances appealing after a need has been created, usually by deprivation or physiological change, for a nutrient contained in the substance (e.g., Bare, 1949; Appledorf and Tannenbaum, 1967). Carnivores, and omnivores that give birth to altricial young, appear primed to ingest all the material expelled, *including* the young. Viable young, however, through vocalization, movement, and warmth, inhibit the mother from ingesting them (Noirot, 1972; Peters and Kristal, 1983; Kristal, 2009; Kristal et al., 2012), and instead, help to trigger the onset of caretaking behavior (Peters and Kristal, 1983; Stern, 1989, 1997; Kristal, 2009).

The *benefits* of placentophagia, the *"ultimate cause"* of ingestion of afterbirth, are quite another matter (Kristal et al., 2012). Unsubstantiated hypotheses in the scientific and popular literature about the benefits of placentophagia, sometimes confusing proximate with ultimate causality, such as nest hygiene, replenishment of nutrients or hormones, "voracious carnivorousness", or avoidance of predators, have been discussed at length previously (Kristal, 1980, 1991). Although the individuals performing the behavior need not be conscious of the benefits, those benefits have adaptive significance in regard to evolution (Tinbergen, 1963; Kristal et al., 2012). Over the past several decades, experimental research (conducted largely in the laboratory of MBK) has elucidated several benefits of parturitional placentophagia that would confer an advantage to those engaging in the behavior at parturition, and one benefit that might be medically useful even beyond a parturitional context.

1.2. Benefits

The most important step in the hypothetical *experimentum crusis* necessary to determine the benefits of placentophagia in nonhuman mammals would be to prevent the mother from ingesting placenta and amniotic fluid at parturition and to examine consequent changes in physiology and behavior. However, although this type of placenta deprivation has been attempted (Grota and Eik-Nes, 1967; Blank and Friesen, 1980), as described in detail previously (Kristal, 1991) their data are questionable because the procedure is virtually impossible to perform successfully without (a) interfering with delivery; (b) allowing for consumption of some amniotic fluid; (c) producing inordinate *stress* in the mother (which would confound the results); or (d) interfering with post-delivery behaviors. As a result of this challenge, our subsequent research employed a variety of methodological techniques to finesse the results.

1.2.1. Attractiveness and maternal behavior

Afterbirth is not usually attractive to nonhuman mammals except as found or scavenged food for some carnivores. Only a very small proportion of virgin rats, mice, or rabbits voluntarily eat foster placenta (Kristal and Williams, 1973; Kristal and Graber, 1976; Kristal and Nishita, 1981; Kristal et al., 1981a; Melo and González-Mariscal, 2003). Yet, at delivery, immediately-prepartum nonhuman mammalian females, even those with no previous birthing experience, are *intensely* attracted to the materials, whether they are carnivorous, herbivorous, or omnivorous (e.g., Kristal et al., 1981a,1981b). As mentioned, this attraction is probably based on a specific hunger for one or more, as yet unresearched, components of the afterbirth. This extreme attractiveness of placenta and amniotic fluid to the puerpera during parturition is actually the first benefit, because by inducing licking of the newborn, it facilitates approach and close contact of the mother with the newborn. This "enforced" proximity and contact help to enhance bonding and help to guarantee the onset of full maternal behavior (Stern, 1997; Anderson et al., 2003), as does reducing the size of the enclosure in which the mother and newborn are housed (Terkel and Rosenblatt, 1971) or coating the newborn with other attractive substances (Kristal et al., 1981b). Experimentally, newborn rats, lambs, and dogs that are covered in afterbirth material are more readily accepted and mothered by experienced adult females than are newborns that are cleaned of their fetal coatings and smells. Furthermore, if *nulliparae* are continuously exposed only to neonates coated with afterbirth material or exposed only to clean neonates, they will all eventually begin mothering them; but those exposed to the afterbirth-coated neonates will begin mothering significantly sooner than will those exposed to clean neonates (Dunbar et al., 1981; Kristal et al., 1981b, 2012; Lévy and Poindron, 1987; Steuer et al., 1987; Abitbol and Inglis, 1997; Kristal, 2009).

1.2.2. Suppression of pseudopregnancy

The second benefit concerns the fact that most mammalian puerperae are impregnated during the postpartum estrus (Thatcher and Wilcox, 1973; Connor and Davis, 1980; Gilbert, 1984). Parturition is accompanied by an upsurge in follicle-stimulating hormone (FSH) and estrogen, and a consequent ovulation and period of behavioral sexual receptivity (estrus). Depending on the species, this postpartum estrus can appear in the mother from minutes to hours after delivery and can last for hours or more. Impregnation during this period depends only on the availability of males. However, a competing process can occur: the tactile/mechanical stimulation caused by the fetoplacental unit passing through and stretching the cervix can result in pseudopregnancy, as could copulation with an infertile male, experimental tactile or electrical stimulation of the cervix, or drug injection (Kisch, 1971; Terkel, 1986; Norris and Lopez, 2010). Pseudopregnancy is the triggering of the hormonal and physiological changes associated with pregnancy in the absence of fertilization, and once initiated, can proceed for more than a third of the gestation period without a conceptus, while preventing copulatory fertilization during that period. Obviously, pseudopregnancy resulting from delivery of a fetoplacental unit is maladaptive for the species. As mentioned, pseudopregnancy can also be triggered in nullipara during estrus by experimental tactile/mechanical vaginal/cervical stimulation. We therefore used this nonpregnant-rat model to demonstrate that placentophagia significantly decreases the probability of pseudopregnancy resulting from experimental vaginal/cervical stimulation during estrus. Among the groups of rats receiving 225 g vaginal/cervical pressure in our pseudopregnancy study, 44% of those that also received an orogastric infusion of saline entered pseudopregnancy,

whereas only 10% of those that also received an orogastric infusion of amniotic fluid became pseudopregnant (Thompson et al., 1991a). Clearly, this is an adaptive advantage for the species because it increases the probability of postpartum fertilization. The mechanism by which placentophagia accomplishes this is not yet understood, but an analysis of hypothalamic responses showed that vaginal/cervical stimulation, when accompanied by orogastric amniotic fluid infusion, produced enhanced c-fos expression in estrus female rats in response to a low level (75 g) of vaginal/cervical pressure that does not, by itself, produce significant c-fos expression. Enhanced c-fos expression, only after coupling 75 g vaginal/cervical stimulation with orogastric infusion of amniotic fluid, was seen in the medial preoptic area (MPOA) and the ventrolateral ventromedial hypothalamus (vlVMH)(Hoey et al., 2011), both of which are critical to, among other things, the onset of maternal behavior (Stack et al., 2002; Mann and Babb, 2004) and the regulation of pseudopregnancy (Peters and Gala, 1975; Northrop et al., 2006). Note that vaginal/cervical tactile stimulation (VS) during estrus also produces opioid-mediated hypoalgesia (Crowley et al., 1976; Gintzler and Komisaruk, 1991), and that this hypoalgesia is enhanced by either placenta ingestion (Kristal et al., 1986b) or amniotic fluid ingestion (Thompson et al., 1991a)(Table 1).

1.2.3. POEF

The third benefit of placentophagia has several branches that may all be attributable to a component of placenta and amniotic fluid that has been termed POEF, for Placental Opioid-Enhancing Factor (Kristal et al., 1988). A summary of the research can be found in Table 1.

1.2.3.1. POEF and pain. We have concluded that the principal function of POEF during parturition, particularly that found in amniotic fluid, which is available before delivery, is *to enhance ongoing endogenous opioid hypoalgesia* ("analgesia of pregnancy" [Gintzler, 1980]) *without liability to the onset and performance of maternal behavior*. We prefer the term "hypoalgesia" to "antinociception" or "analgesia" because in our opinion "antinociception" implies mechanism, whereas "hypoalgesia", i.e., "reduced pain", refers to an objective score only, and "analgesia" technically means "*no* pain" at all. Table 1 shows that POEF activity was found in the afterbirth of several species (rat, cow, dolphin, human) when tested in a variety of rodent algesiometric assays (Kristal et al., 2012, for additional review), and POEF activity in bovine amniotic fluid has even been demonstrated in an ingenious cow algesiometric test (Pinheiro Machado et al., 1997). If maximal hypoalgesia during parturition were accomplished simply by increasing the amount of endogenous opioid available, that elevated level of opioid activity could disrupt the performance of maternal caretaking behavior (e.g., Bridges and Grimm, 1982; Rubin and Bridges, 1984; Tarapacki et al., 1995; Miranda-Paiva et al., 2001) and would likely result in other undesirable side effects such as depressed respiration and inhibited gut-transit time. However, it seems that enhanced opioid-mediated hypoalgesia induced by POEF is selective to some opioid effects (e.g., hypoalgesia), but not others (e.g., constipation, hyperthermia)(Kristal et al., 1990b; Thompson et al., 1991b; Corpening et al., 2004; DiPirro and Kristal, 2004). We want to emphasize that although afterbirth contains some opioids, in all tests for hypoalgesia enhancement, placenta or amniotic fluid ingestion – in the absence of underlying elevated endogenous or exogenous opioids – has no hypoalgesic effect; therefore, *POEF itself is not an analgesic*, but must work by enhancing ongoing opioid activity (for review, see Kristal, 1991 and Kristal et al., 2012). POEF shows dose-dependent activity in rats that is independent of volume (Kristal et al., 1988). The optimal "doses" for rats are 1 placenta (500 mg) and 0.25 ml amniotic fluid; these are roughly the amounts available during the expulsion of one feto-placental unit. In mature cows, the POEF effect was demonstrated by orogastric infusion of 1.5 kg of amniotic fluid (Pinheiro Machado et al., 1997)(see Table 1), but other volumes were not tested. Obviously, different species would have different dose requirements and may have different dose-response curves for POEF. The effect of varying the dose of POEF in conjunction with varying the dose of exogenous opioid has not been systematically examined. However, a synthesis of all our work on various doses of POEF with various doses of morphine and vaginal stimulation-induced hypoalgesia tends to suggest that the effect of POEF on doses of endogenous and nonselective exogenous opioids may be an inverted-U-shaped function. In this way, POEF may be "self-limiting", possibly due to differential effects on different central opioid-receptor species or on different central sites.

The mechanism of POEF action seems to be elegantly well suited to operate during parturition. POEF is present in amniotic fluid, and therefore is available to parturient mothers *before* the delivery of the first neonate, or only neonate (monotocous species). To mothers delivering litters (polytocous species), both amniotic fluid and placenta are available to provide POEF before and throughout the entire delivery (Kristal, 1991). Furthermore, POEF, itself, is apparently not absorbed into the system and must be ingested to work: first, systemic injection (1.0 ml amniotic fluid, IP or SC) was not effective in producing a POEF effect (Abbott et al., 1991); and second, the POEF effect requires intact gastric vagus afferents (Tarapacki et al., 1992; Robinson et al., 1995)(see Table 1). One apparent outlier in the literature is a study conducted in mice, in which a large *intraperitoneal* injection of "human placental extract" (also called HPE, and marketed as Placentrex®) was observed to enhance morphine hypoalgesia (Gurgel et al., 2000). In the manufacture of Placentrex, the extract is heated to 120 °C under pressure several times, in order to inactivate the HIV virus (Albert David: Placentrex [website]). POEF, however, is rendered inactive by heating to more than 40 °C (Kristal et al., 2012). Therefore, it is most likely that the enhanced hypoalgesia observed in the Gurgel et al. study was produced by the additive effect of morphine and the *opioid content* of the placenta extract (Petraglia et al., 2006), and not by POEF.

Once in the stomach, POEF may work by affecting chemically sensitive receptors of the gut-brain system (Vergnolle, 2005; Bellono et al., 2017; Kaji and Kaunitz, 2017). Afferent neural transmission of the POEF signal apparently then travels up the vagus nerve and produces an exclusively *central* enhancement (DiPirro et al., 1991) of δ- (Fig. 1) and κ-opioid-mediated hypoalgesia, and an attenuation of μ-opioid-mediated hypoalgesia (Fig. 2) (DiPirro and Kristal, 2004). These properties of POEF fit well with the physiology of endogenous opioid systems during pregnancy and parturition, when there is a downregulation of μ receptors (Hammer et al., 1992) and an increase in δ/κ receptor activity and in endorphins (Csontos et al., 1979; Wardlaw and Frantz, 1983; Räisänen et al., 1984; Dawson-Basoa and Gintzler, 1998; Gintzler et al., 2008). Note that it is predominantly μ-opioid-receptor activity (compared to δ- and κ-opioid activity) that disrupts maternal behavior (Mann et al., 1991) and mediates many of the unwanted side effects of medical opioids, such as tolerance/addiction, constipation, and respiratory depression (for review, see Wang, 2019). A POEF/vagus mechanism helps to explain the very rapid effect; orogastric infusion of amniotic fluid was observed to enhance morphine-mediated hypoalgesia within 5 min, and to last, in rats, for a period that corresponds to a bit longer than the average inter-pup interval during delivery (Doerr and Kristal, 1989). Vagal afferent stimulation has already been implicated in opioid-mediated hypoalgesia (Randich and Gebhart, 1992; Bohotin et al., 2003a, 2003b; De Couck et al., 2014; Komisaruk and Frangos, 2021) and has been shown to result in increased opioid-receptor activity, particularly δ-receptor activity (Hu et al., 2021). POEF may prove to be a naturally-occurring chemical stimulus that feeds into this vagal mechanism.

POEF seems to exist only in afterbirth tissue (Abbott et al., 1991) and is therefore not produced in males; however, male rats can experience enhancement of hypoalgesia produced by POEF ingestion (see Table 1). In male rats that received an intraperitoneal injection of morphine, the morphine hypoalgesia was significantly greater in the males that received a concurrent orogastric infusion of amniotic fluid than it was in those that received a concurrent orogastric infusion of beef bouillon

Table 1
Results of Tests for POEF Effects and Possible POEF Effects. (Abbreviations: AF = amniotic fluid; IC = intracerebral; ICV = intracerebroventricular; IP = intraperitoneal; MS = morphine sulfate; pla = placenta; SC = subcutaneous; OG = orogastric; VS = vaginal/cervical stimulation. Placenta was voluntarily eaten. Female rats tested unless otherwise noted.).

Test Used	Opioid Administered	Opioid Receptor	Afterbirth Administered	Effect	Reference
Hind-paw shock	Endogenous only		$\overline{X}$= 3.9 pla	Enhanced footshock hypoalgesia	(Kristal et al., 1985)
Radiant heat tail flick	3 mg/kg MS, IP	Nonspecific, mostly μ	$\overline{X}$= 1.67 pla	Enhanced MS hypoalgesia	(Kristal et al., 1985)
Radiant heat tail flick	75 g VS, endogenous only		3 pla (1.5 g)	Enhanced VS hypoalgesia	(Kristal et al., 1986b)
Radiant heat tail flick	3 mg/kg MS, IP	Nonspecific, mostly μ	1.0 ml AF (OG infusion)	Enhanced MS hypoalgesia	(Kristal et al., 1986a)
Radiant heat tail flick	3 mg/kg MS, IP	Nonspecific, mostly μ	Various doses of placenta	Optimal enhancement with 1 pla	(Kristal et al., 1988)
Radiant heat tail flick	3 mg/kg MS, IP	Nonspecific, mostly μ	Various doses of AF (OG infusion)	Optimal enhancement with 0.25 ml AF	(Kristal et al., 1988)
Hot water tail dip	Labor, endogenous only		0.25 ml AF (OG infusion)	Enhanced labor hypoalgesia	(Kristal et al., 1990b)
Formalin test	3 mg/kg MS, IP	Nonspecific, mostly μ	0.25 ml AF (OG infusion)	Enhanced MS hypoalgesia	(Kristal et al., 1990a)
Formalin test	None, only aspirin, IP + naltrexone, SC		0.25 ml AF (OG infusion)	No enhancement of aspirin hypoalgesia	(Kristal et al., 1990a)
Hot water tail dip	125 g VS, endogenous only		0.25 ml AF (OG infusion)	Enhanced VS hypoalgesia	(Thompson et al., 1991a)
Hot water tail dip	225 g VS, endogenous only		0.25 ml AF (OG infusion)	Fewer pseudopregnancies	(Thompson et al., 1991a)
Radiant heat tail flick	2.5 μg MS, ICV + systemic quaternary naltrexone	Nonspecific, mostly μ	0.25 AF (OG infusion)	Enhanced central (not peripheral) MS hypoalgesia	(DiPirro et al., 1991)
Radiant heat tail flick	3 mg/kg MS, IP, for 10 days. Day 12, challenge dose of 1.5 mg/kg MS, IP	Nonspecific, mostly μ	0.25 AF (OG infusion)	Enhanced MS hypoalgesia and reduced withdrawal symptoms with a subthreshold dose of MS	(Doerr and Kristal, 1991)
Radiant heat tail flick (males)	3 mg/kg MS, IP	Nonspecific, mostly μ	2 pla (1 g)	Enhanced MS hypoalgesia in *male rats*	(Abbott et al., 1991)
Radiant heat tail flick	VS-induced, endogenous only		0.5 g *human* pla PM30 cytosolic filtrate (OG infusion)	Enhanced VS hypoalgesia	(Abbott et al., 1991)
Radiant heat tail flick	VS-induced, endogenous only		0.5 g *dolphin* pla YM5 cytosolic filtrate (OG infusion)	Enhanced VS hypoalgesia	(Abbott et al., 1991)
Contralateral circling after unilateral injection	MS, various doses, IC, into VTA	Nonspecific, mostly μ	0.25 ml AF (OG infusion)	Inhibition of contralateral rotation	(Thompson al., 1991b)
Radiant heat tail flick	VS-induced, endogenous only		0.5 g pregnant rat liver	No enhanced VS hypoalgesia	(Abbott et al., 1991)
Radiant heat tail flick	3 mg/kg MS, IP	Nonspecific, mostly μ	1 ml AF, SC or IP	No enhanced MS hypoalgesia	(Abbott et al., 1991)
Body temperature	Various doses of MS, IP	Nonspecific, mostly μ	0.25 AF (OG infusion)	No change in body temp beyond MS hyperthermia	(Abbott et al., 1991)
Radiant heat tail flick + gastric vagotomy	1 mg/kg MS, IP	Nonspecific, mostly μ	1 pla (0.5 g)	No enhanced MS hypoalgesia	(Tarapacki et al., 1992)
Radiant heat tail flick + maternal behavior test	2 mg/kg MS, IP 3 mg/kg MS, IP	Nonspecific, mostly μ	0.25 AF (OG infusion)	Enhanced MS hypoalgesia, No interference with maternal behavior	(Tarapacki et al., 1995)
Radiant heat tail flick	VS-induced, endogenous only		5 mg/kg famotidine (OG infusion) + 1 pla	Enhanced MS hypoalgesia	R,A,K 1995
Hotplate	None, only nicotine, SC + naltrexone, SC		0.25 ml AF (OG infusion)	No enhanced nicotine hypoalgesia	(Robinson-Vanderwerf et al., 1997)
Foot-lift after thermal stimulation	0.08 ml/kg, IV	Nonspecific, mostly μ	1.2 kg *bovine* AF (OG infusion)	Enhanced MS hypoalgesia in *cows*	(Pinheiro et al., 1997)
Radiant heat tail flick	3 mg/kg MS, IP	Nonspecific, mostly μ	0.5 ml bovine AF (OG infusion)	Enhanced MS hypoalgesia	(Corpening et al., 2000)
Hotplate	Various doses of DPDPE, ICV	δ	2 pla	Enhanced DPDPE hypoalgesia Enhanced DPDPE circling	(DiPirro and Kristal, 2004)
Hotplate	Various doses of DAMGO, ICV	μ	2 pla	Attenuated DAMGO hypoalgesia	(DiPirro and Kristal, 2004)
Hotplate	Various doses of spiradoline, ICV	κ	2 pla	Slight enhancement of spiradoline hypoalgesia at 100 nmol	(DiPirro and Kristal, 2004)
Gut transit time	20 μg MS, ICV	μ effect examined	1 pla	Disinhibition of gut transit (anti-MS effect)	(Corpening et al., 2004)
Maternal behavior	Various doses of MS, IC, into VTA	Nonspecific, mostly μ	0.25 ml AF (OG infusion)	Less MS needed to facilitate maternal behavior onset	(Neumann et al., 2009)
c-fos expression	75 g VS-induced, endogenous only		0.25 ml AF (OG infusion)	Greater c-fos expression than VS alone	(Hoey et al., 2011)
Hot water tail dip	3 mg/kg MS, IP, for 10 days	μ effect examined	0.25 ml AF (OG infusion) for the 10 days of MS injection	Blocked formation of MS tolerance	(Neumann, 2011)
Cold water tail dip	50 ng DPDPE, ICV	δ	0.25 AF (OG infusion)	Enhanced DPDPE hypoalgesia	(Thompson et al., 2018)

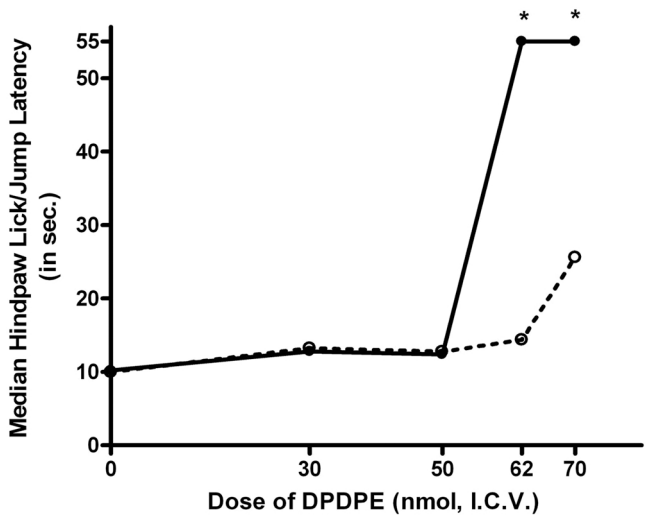

Fig. 1. Enhancement by placenta ingestion of δ-opioid receptor-mediated antinociception. Female rats were fed 1.0 g placenta (•) or control substance (○) 10 min before they were injected with DPDPE (0, 30, 50, 62, or 70 nmol, ICV). Pain threshold is represented by median response latency (in sec) on a 52 °C hotplate test 10 min after DPDPE injection ($n = 5–8$ rats/group). * = significantly different from control-fed group at the corresponding DPDPE dose ($p < 0.05$, median test).
(DiPirro and Kristal, 2004: reprinted with permission from Elsevier).

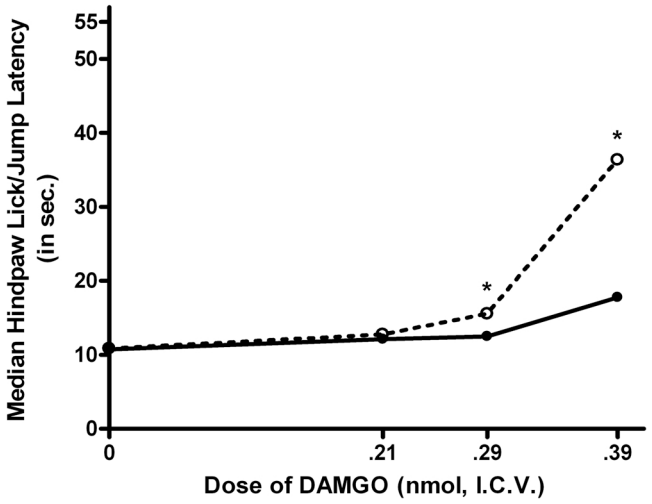

Fig. 2. Attenuation by placenta ingestion of μ-opioid receptor-mediated antinociception. Female rats were fed 1.0 g placenta (•) or control substance (o) 10 min before they were injected with DAMGO (0, 0.21, 0.29, or 0.39 nmol, ICV). Pain threshold is represented by median response latency (in seconds) on a 52 °C hotplate test 30 min after DAMGO injection ($n = 11 – 13$ rats/group). *Significantly different from control-fed group at the corresponding DAMGO dose ($p < 0.05$, median test).
(DiPirro and Kristal, 2004) reprinted with permission from Elsevier).

(Abbott et al., 1991). This, in addition to the presence of POEF activity in afterbirth of various taxonomic groups, suggests to us that the POEF effect may be a universal mammalian phenomenon.

POEF specifically enhances *opioid*-mediated hypoalgesia, but not that produced by either aspirin or nicotine in rats primed with naloxone to block opioid-mediated activity (Kristal et al., 1990a; Robinson-Vanderwerf et al., 1997)(see Table 1). These results support DiPirro's findings that POEF works centrally on specific opioid-receptor types (DiPirro et al., 1991; DiPirro and Kristal, 2004). The POEF effect can be very powerful. As a methodological choice, however, most of our experiments deliberately minimized the effect so as to avoid ceiling responses in timed algesiometric assays. But POEF can easily increase the dependent variable (e.g., latency to respond to a noxious stimulus) by 100–500% over the baseline opioid hypoalgesia level (e.g., DiPirro and Kristal, 2004), which would correspond to a *much larger* dose of opioid.

1.2.3.2. POEF, the VTA, and maternal behavior. What we refer to as maternal behavior, especially in nonhuman mammals, is a reliable constellation of small behaviors that appears to unfold as a smooth, sequenced, integrated whole, functioning to nurture, clean, protect, and feed the young. The details of the behaviors differ depending on the ecological niche of the species (Lehrman, 1961; Gubernick and Klopfer, 1981; Kristal, 2009; González-Mariscal and Melo, 2013; Lévy, 2016).

The brain circuitry for maternal behavior, the "maternal neural substrate" (Moltz, 1966), or "maternal brain network" (Numan and Young, 2016), is widespread and complex because maternal behavior requires sensory input, cognition, motor output, motivation and reward, emotion, and learning and memory. There is a great deal of literature devoted to describing the overall neural circuitry of maternal behavior (e.g., Numan, 2006; Numan and Young, 2016; Kohl and Dulac, 2018), but part of the motivation and reward system involved in maternal behavior, as in other behaviors, is the mesolimbic dopamine system. This mesolimbic system, which uses dopamine as the primary neurotransmitter, includes the ventral tegmental area (VTA) (for review, see Morales and Margolis, 2017). Increased opioid activity in the VTA facilitates both the onset and maintenance of maternal behavior, presumably by accentuating the rewarding aspects, to the mother, of performing and accomplishing the behavior. Increasing the opioid activity in the VTA by microinjecting morphine (0.03 μg) directly into the VTA significantly shortened the latency to the onset of maternal caretaking behavior toward foster young in maternally naïve female rats. Conversely, reducing opioid activity in the VTA by microinjecting the opioid antagonist naltrexone methobromide (quaternary naltrexone – which does not cross the blood-brain barrier) directly into the VTA interfered with the maintenance of maternal behavior in primiparous rats that had been separated from their young for a time (Thompson and Kristal, 1996). A follow-up study showed that when orogastric infusion of amniotic fluid was added to the design, and various doses of microinjected morphine were tested, a significantly *smaller* dose of morphine in the VTA (0.01 μg) produced that same shortening of the latency to the onset of maternal behavior when that dose was coupled with an orogastric infusion of amniotic fluid, but not when it was coupled with a control orogastric infusion (Neumann et al., 2009)(Table 1).

We should note that the effect of POEF on the facilitation of maternal behavior may operate on two levels (see Fig. 3). One is through the VTA/dopamine/reward system just mentioned. The other may be through the facilitative effect of POEF, particularly in parturient females, on the cellular activity of hypothalamic areas that are known to be involved in maternal behavior and that respond to vaginal/cervical stimulation, which is transmitted ultimately by vagal afferent fibers (Graber and Kristal, 1977; Keverne et al., 1983; Hoey et al., 2011; Komisaruk and Frangos, 2021).

1.2.3.3. POEF and withdrawal and tolerance. If POEF enhances morphine-induced hypoalgesia, that is, allows a smaller amount of morphine to have a greater pain-relieving effect, one might expect that a smaller amount of morphine, coupled with ingestion of POEF (in amniotic fluid or placenta), would ameliorate the withdrawal effects produced by abstinence in morphine-tolerant rats. This is, in fact, what happens. When morphine-tolerant rats (made tolerant by receiving either 3 or 4 mg/kg morphine sulfate, IP, for 10 consecutive days) were tested for pain threshold after two days of abstinence, a *subthreshold* dose of morphine (1.5 mg/kg, IP), in conjunction with an orogastric infusion of amniotic fluid (0.25 ml), reversed the hyperalgesia that is

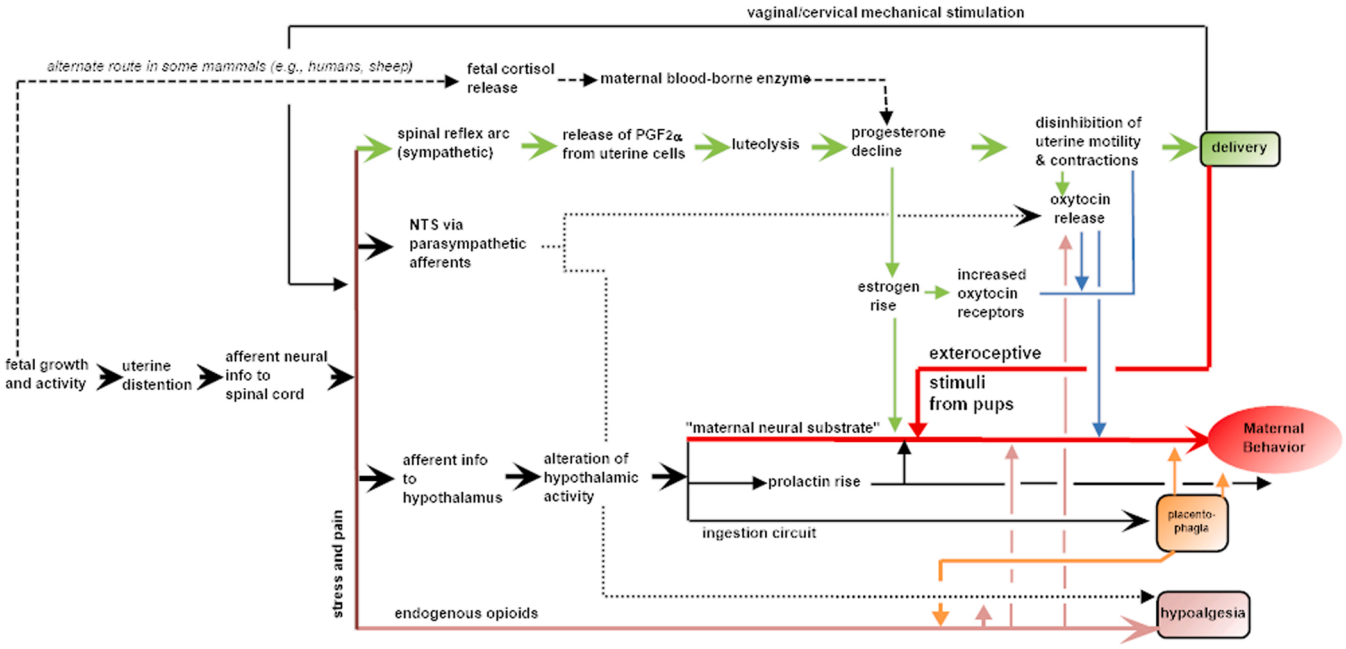

Fig. 3. Diagram illustrating how placentophagia fits into parturitional processes. (Kristal et al., 2012, reprinted with permission from www.tandfonline.com).

characteristic of withdrawal, whereas the 1.5 mg/kg morphine injection in conjunction with an orogastric infusion of saline did not reverse that hyperalgesia (Doerr and Kristal, 1991) (Table 1).

In addition, a daily injection of 3 mg/kg morphine sulfate, IP, (a low, suprathreshold dose) for 10 days, in conjunction with the orogastric administration of amniotic fluid, attenuated the *formation* of tolerance produced by 3 mg/kg morphine alone (Neumann, 2011). The pain thresholds (tail-flick latencies) of the rats treated with amniotic fluid + morphine were significantly higher (indicating less pain) than those of rats treated with saline + morphine, after a challenge dose of 3 mg/kg morphine on Day 11, suggesting that the rats treated with amniotic fluid + morphine were less *tolerant* to the hypoalgesic effect of the morphine than were the controls. Whether amniotic fluid ingestion would block or enhance tolerance formation in rats receiving 10 days of a *subthreshold* dose of morphine has yet to be determined.

1.2.3.4. Summary. Empirical research on placentophagia in nonhuman mammals has shown that the behavior has a set of benefits that are of central importance at parturition to *all* nonhuman (placentophagic) mammals. These may be in addition to the many hypothesized, but untested, benefits in the literature that would apply to only *some* taxonomic groups, such as nest-site cleanliness; replenishment of nutrients or hormones; general hunger; and avoidance of predators (Lehrman, 1961; Kristal, 1980). The set of benefits we have demonstrated, which may not be exhaustive, include (a) facilitation of the onset of caretaking behavior due to the attractiveness, to the mother, of afterbirth materials on the neonate; (b) suppression of pseudopregnancy, thereby increasing fertility; and (c) enhancement of endogenous opioid-mediated hypoalgesia (and some other central opioid-mediated processes) at delivery, without liability to maternal behavior and without the negative side effects that would be generated by higher levels of opioids in the system (i.e., producing more opioid effect from less opioid). We have proposed that at least this last benefit is accomplished by ingesting Placental Opioid-Enhancing Factor – POEF – in placenta and amniotic fluid. POEF ingested during placentophagia seems to have an almost immediate effect on receptors of gastric vagal afferents, the information about which is sent to the brain via vagal connections that are many and diffuse after leaving the nucleus tractus solitarius (e.g., locus coeruleus, raphe nuclei, periaqueductal grey [and therefore the descending pain pathway], and indirectly to hypothalamus, amygdala, and cortex.) In the brain, those vagus signals are translated into enhanced δ- and κ-opioid-receptor activity, and attenuated μ-opioid-receptor activity. Note that although δ- and κ-opioid agonists produce hypoalgesia in males, δ- and κ-opioid systems seem to be more important in female hypoalgesia (Stoffel et al., 2005; Dahan et al., 2008; Gintzler et al., 2008; Sharp et al., 2022), especially during the pain of labor and delivery (Gintzler et al., 2008).

For nonhuman mammals, POEF, and the act of placentophagia that delivers it to the mother, therefore, help to lock together the pieces of behavior into a harmonious whole in which the mother's internal and external environments are coordinated to produce the optimal milieu for the survival of the young and the species.

We have concluded that the importance of POEF likely extends far beyond nonhuman parturitional pain relief, though. As mentioned, POEF activity has been found in the afterbirth of a wide variety of species, perhaps all mammalian placenta and amniotic fluid. That, and its effectiveness in males (rats), suggests that if isolated, characterized, and synthesized, POEF may provide an important adjunctive therapy (in conjunction with subthreshold doses of exogenous opioids, or in conjunction with elevated endogenous opioids) as a novel and natural approach in the medical and veterinary treatment of pain and tolerance.

2. Placentophagy in humans and POEF

Ingestion of afterbirth by humans is conventionally referred to as "placentophagy" rather than "placentophagia", although the meaning is the same. "Placentophagy", and terms like "coprophagy", "anthropophagy", and "polyphagy" are more commonly found in anthropological literature, and usually apply to humans. "Placentophagia", and terms like "hyperphagia", hypophagia", "aphagia", and "polyphagia" are more commonly found in behavioral neuroscience literature, and usually refer to nonhumans as well as humans. Herein we use the term "placentophagy" when referring to human behavior because the overwhelming proportion of work in humans dictates it.

2.1. Placentophagy in the past

The two main investigations of anthropological records regarding placentophagy and related topics in present and past human cultures both showed that, in contrast to anecdotes and urban legends, and in contrast to the previously stated passage by O'Leary, placentophagy was virtually non-existent as a cultural practice before the mid-20th century (Kristal, 1980; Young and Benyshek, 2010). In fact, most cultures regarded placentophagy as taboo, often because it was considered cannibalistic. It is now fairly well known that some cultures regard the afterbirth as sacred and bury it at the roots of a tree or bush, and later brew tea from the leaves or eat the fruit, ritually (Kristal, 1980; Young and Benyshek, 2010); perhaps this serves as a behavioral metaphor for placentophagy. There are rare exceptions, such as famine, disaster, or individual or group starvation, that may lead individuals to engage in placentophagy, but in such circumstances they may also engage in outright cannibalism (Ober, 1979; Kristal, 1980; Young and Benyshek, 2010; Kristal et al., 2012). One exception often cited in pro-placentophagy literature as evidence of human placentophagy is the use of human placenta in Traditional Chinese Medicine. Dried, powdered, human placenta (*Zi He Che*) is indeed used in Traditional Chinese Medicine (Kristal, 1980; Young and Benyshek, 2010), but it is not used alone (Rootdown.US [website]), it is not specifically used on the periparturitional mother, and it is one of a vast variety of what we generally consider, in Western medicine, to be "unusual" substances used for various maladies: antelope horn or pearls for epilepsy; Chinese date (jujube) for attention-deficit/hyperactivity disorder (ADHD); or turtle shell for cancer (Kristal, 2012 [website]). Not many of the thousands of Traditional Chinese Medicine preparations have been tested empirically for efficacy, and contrary to New Age wisdom, not all those that have been tested are actually effective. Furthermore, when there has been empirical testing of these medicinal preparations, the resulting information has often been of poor quality (Li et al., 2014). Hypotheses about the reasons for humans or pre-humans abandoning placentophagy at some point in the evolutionary past have been discussed in some detail previously (Kristal et al., 2012; Young et al., 2012). However, when looking for motivation for an obscure behavior, whether there is real logic (e.g., accurate deduction), faulty logic (e.g., superstition), or no logic (let's see what happens), it is important to bear in mind, as mentioned previously (Kristal et al., 2012), that "…someone in the past, present, or future, has done, is doing, or will do, anything conceivable to the human mind". As an extreme example, search the internet for a "man who ate an airplane.".

2.2. Placentophagy in the present

Prior to the late 1960s, evidence of placentophagy was anecdotal, second-hand at least, and represented exceptions (Young and Benyshek, 2010; Kristal et al., 2012). In the late 1960s and early 1970s – the "hippie" era – there were many reports of individuals or groups eating raw or cooked human placenta. The attitude seemed to be "Animals do this, we are animals, we should do this", in contrast to the anthropological finding that seemed to suggest that non-western cultures thought "Animals do this, we are not animals, we should not do this" (Kristal, 1980; Young and Benyshek, 2010; Kristal et al., 2012). During that era, placentophagy seemed to be part of a general back-to-nature movement, which later morphed into the New Age home-birthing phenomenon (Bean, 1977).

> "I stood looking doubtfully at the small piece of sautéed placenta on a toothpick…. Refusing this ceremonial gesture was just something I could not do….an earlier suggestion of a paté on crackers might have been preferable.
>
> 'We'll have the rest of it in stew tonight. I'll get my iron that way,' announced Beth…'It's the only meat one can get without killing an animal,' she added." (Bean, 1977, p. 75)

To be sure, human puerpera are not intensely attracted to afterbirth materials, as are their nonhuman counterparts. In fact, terms like "disgust "and "revulsion" are often used to describe the mother's reaction to the idea of afterbirth consumption (Dickenson et al., 2017). We don't know whether these reactions are biologically or culturally programmed, but clearly, the specific-hunger process is not in operation in modern human parturition.

Based on recommendations of midwives and doulas, and then by representatives of placenta-preparation companies, women in affluent countries, particularly in the United States starting in the 1980s, began eating their placentas in order to derive what they assumed were real health benefits (e.g., Soyková-Pachnerová et al., 1954; Janszen, 1980; Field, 1984; Kristal et al., 2012; [Placenta Lady - Jody Selander (website) 2022; Placenta Practice – benefits (website); Placenta Practice – faqs (website)]), and were occasionally based on benefits reported for nonhuman mammals (e.g., Placenta Benefits (website) 2019, ⟨https://placentabenefits.info/placentophagys-biological-purpose/⟩. (accessed 5/15/22).). This phenomenon became much more widespread as the internet and social media became ubiquitous. In 2013, in what may have been the first scientifically administered questionnaire on the subject, women who had engaged in placentophagy were surveyed for their subjective impressions (Selander et al., 2013). Among the benefits *sought and expected* by the subjects, the greatest was mood improvement, followed by "other" and "unspecified" benefits, with small proportions claiming a motivation for recovery from birth, the restoration of hormones and nutrients lost during pregnancy and delivery, and finally, improved lactation. There are also reports in the literature that human placentophages expect that the practice will *prevent* postpartum depression, pain, etc. (Odent, 2014; Coyle et al., 2015; Farr et al., 2017; Benyshek et al., 2018). It is very difficult, except perhaps using epidemiological methods with huge samples, to determine what events, conditions, or diseases that do not occur with regularity might actually be *prevented* by doing something in particular (a belief that often gives rise to superstitious behavior [Beck and Forstmeier, 2007]). On a small scale, and with the same success, claims of prevention might just as likely include events such as elephant stampedes and solar eclipses. In the same 2013 study, the placentophages were asked what benefits they *felt* they *derived* from the practice (Selander et al., 2013). Most reported experiencing improved mood, a slightly smaller proportion reported experiencing improved energy, and small proportions reported experiencing improved lactation and attenuated bleeding. Over two-thirds of the respondents reported experiencing no negative side effects, a few were turned off by the sensory qualities of placenta, and a very small proportion reported headaches. The subject cohort in this study consisted overwhelmingly of white, middle-class women, with at least some college education. Seventy-five percent reported that, overall, placentophagy was a positive experience. The placenta they ingested was their own, and reportedly was available to them in one of several different forms: commercially dehydrated and encapsulated from raw placenta; commercially dehydrated and encapsulated from cooked placenta; cooked; raw; or other. Most first- and second-time placentophages used cooked-encapsulated placenta (about 40% overall). The next most common form was raw-dehydrated-encapsulated placenta (about 25% overall). This was followed by "other" forms (e.g., smoothies, cooked, frozen cubes; about 23% overall), and finally fresh raw (about 10% overall). Note: there is some suggestion that the percentage of women ingesting fresh raw placenta is much higher in Europe than in the United States, perhaps as high as 75% of placentophages (A. Münz, unpublished observation, 2020). In the survey study, the amount (dose) of placenta ingested each time, the timing of placentophagy relative to delivery, and the time-course of placenta use, were neither standardized nor assessed (Selander et al., 2013). The recommendations by commercial placenta encapsulators for these parameters are not specific, and usually involve ingesting from one to several capsules (standardized by each preparer) each day until the supply is exhausted (Placenta Practice – faqs [website]; Placenta Lady

[website], 2022). We assume, because it was not examined, that the women in the study had a high expectation of positive results or they would not have engaged in the behavior. Therefore, the placebo effect was at play to some extent. A more recent survey in the United Kingdom (Botelle and Willott, 2020) confirmed the findings of the Selander et al. (2013) study, which had been conducted in the United States.

2.3. Effects of placentophagy

As yet, only one empirical, objective study has been conducted to test whether ingestion of commercially *encapsulated* placenta (cooked and herb-infused) by postpartum mothers actually produced the expected and perceived important benefits of elevation of mood, lessening of fatigue, and increased mother-infant bonding. The conclusion of that double-blind study, using measurements from 10 validated psychometric questionnaires such as the Edinburgh Postnatal Depression Scale (EPDS), The Depression Anxiety Stress Scales (DASS-21), and the Fatigue Assessment Scale (FAS), was that *none* of those effects occurred when encapsulated placenta was taken as recommended and the dependent variables were objectively scored (Young et al., 2018b). In 2019, a group of Canadian researchers (Morris et al., 2019) also attempted to gauge the effect of placentophagy on mood, energy, vitamin B_{12} level, and lactation. Their results showed that placentophagy had no effect on those dependent variables. Although the cohorts were matched for mood, psychotropic medication intake, vitamin supplement intake, and intake of domperidone for lactation, the method of intake varied with 1 subject eating placenta raw and 27 taking (presumably commercial prepared) placenta capsules. Furthermore, 75% of the placenta-exposed subjects took placenta at some unspecified time before postpartum week 1, and the remainder took it between postpartum week 2 and week 4. The number of subjects ingesting placenta in the immediate postpartum period was not reported.

Irrespective of the chemical, nutrient, hormonal, or mineral content of placenta and amniotic fluid (Sánchez Suárez, 2015; Young et al., 2016a, 2016b, 2022), some of which are touted by pro-placentophagy professionals (e.g., True Harmony Wellness [website], 2022; Evidence Based Birth [website], 2022), the important issue is whether placentophagy produces detectable physiological or emotional changes in the mother. One well-controlled study examined the steroid hormone content of the saliva of postpartum mothers as a consequence of ingesting commercially prepared, cooked, *encapsulated* placenta. Those researchers found that despite the hormonal content of the encapsulated placenta, only salivary aldosterone and 17-hydroxyprogesterone, of the 14 steroid hormones assayed, were significantly higher in the placentophagy group than in the placebo group, when encapsulated placenta was taken as recommended (Young et al., 2018a). The same research group also ran a well-controlled study examining whether the high iron content of *encapsulated* placenta, a major selling point on many websites, taken as directed by the encapsulation company, had an effect on the mother's plasma iron level. The data showed that plasma iron levels of the women ingesting encapsulated placenta were not significantly different from those of beef-fed controls (Gryder et al., 2017). Johnson et al. (2018a) found that, in general, the dehydration and steaming process used in commercial placenta encapsulation reduced the levels of the peptide and steroid hormones, minerals (e.g., iron), and bacteria, from the levels present in the pre-processed placental material. More specifically, high temperatures reduce the microbial content of raw placenta to well below the level acceptable for commercial meat in Britain (Johnson et al., 2022). Young et al. (2019) then conducted a study showing that ingestion of encapsulated placenta by puerpera had no effect on postpartum prolactin or neonatal weight gain. Clearly, we can conclude that, so far, encapsulated placenta has been shown to have little or no significant effect, beyond a placebo effect, on the mother when it is ingested in the postpartum period, or afterward.

An extensive study by Sánchez Suárez examined the changes in blood and milk of human mothers who ingested pieces of their *own fresh, raw, untreated placenta* immediately after delivery (Sánchez Suárez, 2015; Sánchez Suárez et al., 2022). Although the amounts of placenta ingested were not standardized (but varied between 200 g and 270 g), the results showed that the blood of the placentophagic mothers at 6 hr postpartum contained significantly higher levels of certain substances, such as vitamin K markers, vitamin A, β carotenes, iron, magnesium, 8 proteins, and 12 amino acids, than did the blood of non-placentophagic mothers (Sánchez Suárez et al., 2022). The milk of placentophages contained significantly higher levels of docosahexaenoic acid, eicosapentaenoic acid, polyunsaturated fatty acids, vitamin K1, and menaquinone 6 than did the milk of nonplacentophages (Sánchez Suárez, 2015). It should be noted that although changes due to placentophagy have therefore been documented in mothers' blood and milk immediately postpartum, the detected increases have not been demonstrated to be physiologically necessary or beneficial.

2.4. Placentophagy and POEF

Although human afterbirth shows POEF activity when tested in rats (Abbott et al., 1991), the studies of human placentophagy have not shed light on whether there is a POEF effect in humans. So far, POEF enhancement of opioid hypoalgesia has been investigated only in nonhuman subjects. Methodologically, algesiometric assessment of pain threshold is still the principal way of testing the POEF effect. The only comprehensive study of placentophagy involving immediately postpartum ingestion of fresh, raw placenta (Sánchez Suárez, 2015; Sánchez Suárez et al., 2022) unfortunately did not include any assessment of pain. In terms of research design, however, unless a pre/post within-subjects comparison, combined with a placenta/placebo between-subjects comparison were used in a pain study, a very large number of subjects would be needed for a simple placenta/placebo between-subjects comparison.

It is unlikely that studies involving encapsulated placenta can contribute to our knowledge of POEF. The literature on nonhuman studies of POEF has shown that for placenta and amniotic fluid to show POEF activity, the tissue must not have been heated too far above body temperature, and should not have been left at room temperature or refrigerator temperature for too long. Furthermore, the dose range of the placenta material must be restricted (Kristal et al., 1988), and the placenta *must* be administered when the subject is experiencing elevated endogenous or exogenous opioid activity (Kristal, 1991; Kristal et al., 2012, for review). The studies involving encapsulated placenta, however, usually involved placental material that was cooked to some extent and infused with "herbs", that has been recommended in a variety of non-empirically-validated doses, and that is administered hours, days, or weeks after delivery (Selander et al., 2013). In order for the POEF effect to be demonstrated in humans, the study would require that various amounts (doses) of raw, fresh, unmodified placenta (or amniotic fluid) be ingested by puerperae during the immediate postpartum period while endorphins are still elevated (Wardlaw and Frantz, 1983; Hammer and Bridges, 1987; Hammer et al., 1992; Jarvis et al., 1997), with an algesiometric test such as the cold-pressor test administered just before and perhaps 15 min after ingestion. (The often-used Wong-Baker faces pain-rating scale is probably not objective enough or reliable enough in this circumstance.) To some extent, endogenous δ- and κ-opioid activity is also elevated during lactation and stimulates prolactin release (Tavakoli-Nezhad and Arbogast, 2010), but conducting an algesiometric test at that time would require placenta that had been frozen and thawed. Testing for the POEF effect in human males would be even more methodologically challenging. First, the male would probably have to be the father of the neonate that is delivered. Second, there would be some difficulty in reliably finding or producing an elevated opioid period in the male that would occur at the same time the placenta or amniotic fluid was fresh. However, the methodological challenges in both the female study and the male study would be reduced considerably once POEF is isolated, characterized, and either extracted or synthesized.

Another challenge to the study of placentophagy in humans is a change in the last several years in the attitude of professionals toward ingestion of placenta, either raw or encapsulated, as a birthing experience. Until recently, ingestion of placenta was regarded by proponents as entirely safe, and in 2007 one of the authors (MBK) was even asked to testify to that point in court; however, he declined because the absolute safety of placenta ingestion in humans had never been assessed, and contamination is always a possibility (Las Vegas Review Journal, 2007 [website]). In 2016, a well-publicized case was reported in which a newborn baby contracted a serious streptococcus B infection from a mother who ingested encapsulated placenta. This event resulted in a recommendation by, among others, the Centers for Disease Control and Prevention (Buser et al., 2017), the *Journal of Obstetrics and Gynecology – Canada* (Elwood et al., 2019), and the *Journal of Obstetric, Gynecologic & Neonatal Nursing* (Hayes, 2016) for women to avoid ingesting encapsulated placenta. Since 2017, websites and articles providing information about placentophagy, whether informational or commercial, have included warnings as well as mentioning benefits (e.g., Farr et al., 2017; Johnson et al., 2018b; Bosco and Díaz, 2018; Taylor, 2022; Hearth and Home Midwifery [website]; What to Expect [website]). However, in 2018, an epidemiological study was conducted on a data set containing pregnancy and parturition records of over 20,000 women. These data showed that among the over 7100 that ingested placenta in some form (9% ingested raw placenta and 85% ingested encapsulated placenta with nearly a 50–50 split between encapsulated uncooked placenta and encapsulated cooked placenta), placentophagy produced no adverse neonatal outcomes (Benyshek et al., 2018). Because of the general change in attitude toward the safety of placentophagy, though, Institutional Review Boards may be more reluctant to approve academic studies of the POEF effect in humans unless safety can be guaranteed by sterilization of the afterbirth material.

3. What is POEF?

Ultrafiltration has shown that the human and dolphin POEF molecule is smaller than 30 kD (Abbott et al., 1991). In addition, dolphin-placenta cytosolic preparation was active after passing through a YM5 filter (Abbott et al., 1991), but rat-amniotic fluid cytosolic preparation was not (unpublished observation). It is possible that different species have POEF molecules of slightly different sizes due to different "decorations" (amino-acid-sequence differences in the translated proteoforms, and subsequent post-translational processing), but our conclusion is that the general size of the POEF molecule is under 30 kD and possibly around 6–8 kD (Kristal et al., 2012). Commercial preparations of acetone-extracted, lyophilized, powdered human and bovine placenta (once available from the former Sigma Chemical Co.) were both found to contain POEF activity (unpublished observations), which led to the conclusion that POEF was not a steroid. Furthermore, POEF is not created in the stomach (Tarapacki et al., 1992; Robinson et al., 1995), but it does seem to survive the extreme acidic environment of the stomach for at least a few minutes (Doerr and Kristal, 1989).

There have been several recent studies conducted, and several new databases created, of the proteomics of human and nonhuman mammalian afterbirth tissues using-cutting edge techniques such as gel electrophoresis, enzymatic digestion of proteins, and liquid chromatography/tandem mass spectrometry (LC-MS/MS)(e.g., Heywood et al., 2017; Liu et al., 2019; Wawrzykowski, 2019; Shao et al., 2021; Bhatti et al., 2022; The Human Protein Atlas, 2022; UniProt, 2022). We hope that a comparison of the proteomics of placenta and amniotic fluid with the proteomics of liver, which does not show POEF activity in rat algesiometric tests (see Table 1), will begin to provide some insights into the characterization of POEF. Further research will reveal whether POEF is a known peptide with a heretofore unknown function, or is an entirely unknown peptide.

4. The future of POEF

If and when POEF is isolated and characterized, assuming it is one or maybe only two molecules, it can then be synthesized and used as an adjuvant for low-dose opioid therapy for pain and addiction. For pain management, POEF could be used in conjunction with low, perhaps subthreshold, doses of exogenous opioids, which should significantly reduce the liability for tolerance and addiction. In cases of chronic or prolonged pain in which endogenous opioids are elevated, such as labor, gynecological pain (e.g., endometriosis, Torres-Reverón et al., 2016), and some types of neuropathic pain (Xu et al., 2004), POEF might even be useful in the complete absence of exogenous drugs, to enhance the hypoalgesic activity of endogenous opioids.

POEF seems to be a unique substance that works through a newly recognized mechanism; POEF exerts its effects on opioid hypoalgesia by regulating the activity of the vagus nerve at peripheral receptors in the stomach, and perhaps nowhere else. The vagal signal is then transmitted to the brain to produce a central effect on opioid receptors. Although there is a growing body of knowledge on the role of vagal activity in the regulation of behavior, including pain, we think POEF is the first proposed biologic to act on the vagus nerve in a selective way. The implications of this novel and natural approach are potentially very important: the development of medications for pain management that are as effective as current “gold standards” but with reduced side effects and lower liability for tolerance and addiction.

As mentioned in Section 1.2.3.1., the possibility exists that POEF may be "self-limiting", in that it may actually inhibit the effects of high doses of non-receptor-specific opioids such as morphine while enhancing these same opioids at lower doses. These seemingly contradictory results are not new to the study of opioid-induced analgesia; recent research suggests that the explanation for this lies in the complex nature of the opioid receptor/G-protein complex, which shows allosteric binding sites, ligand-dependent biased signaling, and a large number of heterodimer structures that regulate the functional outcome of activation by available ligands and opioid drugs (Valentino and Volkow, 2018). As such, the enhancement of DPDPE and inhibition of DAMGO (DiPirro and Kristal, 2004) may be evidence of the POEF-produced effect on non-receptor-specific opioids, as previously mentioned. If this "self--limiting" effect bears out after additional research, POEF may also prove to be beneficial in the treatment of Opioid-induced Hyperalgesia (OIH), or Opioid Hyperalgesia Syndrome, which can result from the use of high doses of opioid (e.g., morphine) in the treatment of chronic pain (Lee et al., 2011; Ingram, 2022).

Useful medicinal biologicals can result from the study of unusual substances: plants, venoms, tissues, etc. POEF may be an important example of this phenomenon given its pronounced behavioral and physiological effects on opioid systems. The study of POEF thus far has revealed a potentially useful substance in placenta and amniotic fluid that greatly, and quickly, augments the hypoalgesic action of opioids. The data also suggest that POEF may reduce opioid-addiction liability by greatly reducing the dose of opioid needed in the treatment of pain, and also might be useful in the treatment of dependence, a symptom of addiction. Rats that are dependent on morphine require less morphine during withdrawal, if the morphine is coupled with ingested POEF (in amniotic fluid), to stave off withdrawal symptoms (Doerr and Kristal, 1991). Opioid-induced dependence after prescription opioid use, and the development of other opioid-misuse behaviors, is an important component in the current opioid epidemic in the United States which, in 2019, affected 1.4 million people (Substance Abuse and Mental Health Services Administration (SAMSHA), 2020). This problem has intensified the search for alternative pain treatments, including the development of adjuvant treatments to reduce the dose of opioid needed to control pain. Pain management continues to be a central focus in healthcare in the United States where the prevalence of acute and chronic pain is greater than 50%, costing more than $550 billion annually (Gaskin and Richard, 2012; Lucas et al., 2021). Opioids remain the most common treatment

for moderate to severe pain. Research suggests that among chronic pain patients, 20–30% develop behavioral problems in response to opioid treatment (e.g., dependence) with up to 12% developing substance-use disorder (Vowles et al., 2015). The ongoing opioid epidemic, which has been sustained in large part by the misuse of prescription opioids (Brummett et al., 2017), underscores the need to continue searching for alternative pain therapies that reduce or remove the need for traditional opioid use. If POEF could be isolated and characterized, it might be extracted or synthesized for development as a medical adjunct to human pain-management therapies. Such a pharmacotherapeutic adjunct could reduce the needed opioid medication to a subthreshold level, which might prevent narcotic tolerance and dependence. It might even be usable to enhance the effects of elevated endogenous opioids to decrease pain in the absence of exogenous narcotics. Furthermore, it might also be useful as an adjunct to tolerance and withdrawal therapies – as with pain therapy, minute doses of opioid in combination with POEF could be used to combat withdrawal and tolerance. POEF has the potential to become a novel, innocuous solution to the problems of using addictive narcotics to control pain and withdrawal, while reducing the tendency to develop tolerance to those narcotics.

5. Conclusions

In nonhuman, nonaquatic, placental mammals, the ubiquitous periparturitional behavior of ingestion of placenta and amniotic fluid, which contain Placental Opioid-Enhancing Factor, provides several significant benefits to the mother including facilitated onset of caretaking behavior of the young, suppressed pseudopregnancy, and enhanced opioid-mediated effects like hypoalgesia. Therefore, in nonhuman mammals, POEF, and the act of placentophagia that delivers it to the mother, help to lock together the pieces of behavior into a harmonious whole in which the mother's internal and external environments are coordinated to produce the optimal milieu for the survival of the young and the species.

In humans, culturally based placenta ingestion, historically, is virtually unknown. In the last few decades, however, placentophagy has been taken up by many in affluent societies as a presumed means of replenishing nutrients, preventing pain and postpartum depression, and facilitating bonding. Controlled empirical research has shown that placentophagy produces none of these effects when placenta is ingested in the popular form of a treated, encapsulated preparation. When raw, untreated placenta is ingested immediately after delivery, biochemical changes occur in the mother's blood and milk, but no physiological need for, or benefit of, these has been established. Nevertheless, even if no biomedical need for placentophagy is forthcoming, the behavior is certain to persist for the foreseeable future if for no reason other than the placebo effect.

Although human placentophagy seems to be unnecessary and we are certainly not advocating it, human afterbirth does show POEF activity when tested in rats; POEF enhancement of opioid hypoalgesia has yet to be tested in humans, where, we feel, it will be effective. We expect that when isolated, characterized, and synthesized, POEF will prove to be a valuable adjunct in the medical management of pain and possibly tolerance and addiction.

Declaration of Conflict Interest

None of the authors has a conflict of interest with any information or products mentioned herein.

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