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Short Communication

On the Relationship Between Placental Opioid-Enhancing Factor and Neuropeptide FF

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Abstract

Both ingested placenta and Neuropeptide FF (NPFF) are known to modify opioid activity. The following mini-review highlights the similarities in the function of ingested placenta and NPFF, and suggests that NPFF may be a key peptide mediating the CNS-based actions of ingested placenta. There is an advantage to understanding the mechanism of ingested placenta's modification of opioid activity, in that such understanding may contribute to alternate pain-management strategies.

Keywords: Analgesia; Antinociception; Neuropeptide FF; Opioid pain; Placenta; Placentophagia

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Kristal, Thompson, & Griskat [1] demonstrated in 1985 that ingested placenta enhances in rats the antinociception produced by exogenous and endogenous opioids, and similar enhancement was subsequently demonstrated with ingested amniotic fluid [2].

Shortly after these discoveries, researchers began using the term POEF (Placental Opioid-Enhancing Factor) to refer to the component of afterbirth material that initiates this enhancement [3]. These demonstrations of the POEF effect were important because they provided an answer to the yet-unresolved question as to why mammals of many taxa, including herbivores, engage in placentophagia (ingestion of afterbirth materials) at parturition [4]. The idea that placentophagia at parturition enhances the endogenous opioid antinociception associated with late pregnancy [5] and parturition was, and still is, considered significant in understanding the proximal and ultimate causes of placentophagia as a reproductive behavior.

The research in the years following the discovery of POEF revealed many characteristics of POEF function, and the following, although not a thorough review, highlights facts on POEF function that are pertinent to the present discussion. Ingested amniotic fluid enhances CNS, but not PNS, opioid-mediated antinociception in rats [6]. An intact vagus nerve is necessary for the POEF effect [7], so POEF probably works by neural receptors in the upper gastrointestinal tract, and likely involves the nucleus of the solitary tract (NTS), the hindbrain nucleus to which the vagus nerve projects. The POEF effect is dose-dependent, being influenced by the level of background antinociception [8] as well as by the quantity of POEF [3]. Finally, ingested placenta may actually attenuate opioid processes rather than enhance them, depending on which type of opioid receptor mediates the opioid activity; specifically, ingested placenta enhances the antinociception produced in rats by selective CNS activation of either κ- or δ-opioid receptors, but attenuates that produced by selective CNS activation of μ-opioid receptors [9]. This latter point was recently supported by the observation that ingested placenta blocks the μ opioid receptor-mediated constipation produced in rats by centrally administered morphine [10]. The studies cited above also show that POEF, ingested as placenta or amniotic fluid, has no effect on antinociception independent of underlying opioid activity.

At about the same time that the POEF effect was initially demonstrated, other researchers identified a new opioid-modulating octapeptide, Neuropeptide FF (NPFF), which was first identified in bovine brain [11] but has since been identified in other vertebrates [12-14]. NPFF is believed to modify, by way of its own G-protein receptors [15,16], the function of same-neuron opioid receptors [17], thereby indirectly modifying opioid function. An understanding of NPFF function, as well as that of other opioid-modulating peptides, is considered important in that such understanding may elucidate the mechanisms of opioid tolerance and dependence [18]. There are other characteristics of NPFF function and distribution, though, that make NPFF a candidate for a key peptide in the CNS-based portion of the POEF effect.

Neuropeptide FF neurons are believed to be located predominantly, if not exclusively, in the CNS, with cell soma based primarily in the hypothalamus and the NTS [19] of rats. NPFF neurons have also been identified, though, in the spinal cord as intrinsic [20] and supraspinal [19] in origin. Although the evidence is not unequivocal, NPFF has been shown to have no effect independent of opioid activity, even though it can reverse the analgesia produced by coinjected morphine [21]. Furthermore, the effect of NPFF has been shown to be dose-dependent [22] and may be site-dependent [23]. Of particular importance is the evidence that NPFF attenuates μ-receptor- mediated activity [11,24-26] and enhances δ-mediated activity [24,25]. Finally, NPFF neurons are known to project to areas of the brain and spinal cord that are involved in antinociception [12,27,28].

The evidence indicates that the characteristics of NPFF function are consistent with those of POEF function. It is reasonable to speculate, then, that NPFF may be a key participant in the opioid-modulating effect of POEF. As ingested placenta or amniotic fluid activates vagal afferent neurons that project from the upper gastrointestinal tract to the NTS, those neurons could then influence

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NPFF neurons based in the NTS. These NPFF neurons, in turn, could modify opioid receptor function in one or more of the antinociception-related nuclei to which they project, thereby influencing spinal or supraspinal nociceptive neurons [21] and consequently modifying opioid antinociception. This same explanation of POEF function could also explain the reversal of morphine-produced constipation that was recently demonstrated in rats that ate placenta [10]. NPFF neurons that project from the NTS to the contralateral NTS [19] may modify hindbrain influences on gastrointestinal function in response to POEF signals through gastrointestinal vagal afferent neurons.

Understanding the neural mechanism of the POEF effect may prove beneficial in ways yet unforeseen by researchers in the field of pain management. Understanding the mechanism of placental modulation of opioid function could conceivably contribute to the development of adjunct treatments for pain that enhance the desirable, while actually blocking the undesirable, CNS-based effects of opioids. Maybe even more appealing, though, is the idea that administration of such adjunct treatments could be as simple as a patient's swallowing a pill.

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