“Bio-communication” Between Mother and Offspring: Lessons From Animals and New Perspectives for Brain Science

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Abstract. Early brain development has a tremendous impact on the success of humans throughout their lives. During early development, neural circuit formation proceeds in a strictly regulated manner. In addition to genetic and epigenetic programs, recent studies using animal models have demonstrated that certain maternal bio-active agents are essential for normal neural development, with deficiencies adversely affecting offspring brain function and behavior. On the basis of these findings, we propose a new viewpoint: that maternal bio-active substances support the development of the fetal and neonatal brain, and the subsequent expression and maintenance of higher brain functions. We term these molecular-based biological conversations between mother and offspring “bio-communications”. Based on findings obtained primarily from animal models, we review the effects of maternal substances on the neural developments and functions. Clarifying the regulatory mechanisms of “bio-communications” will help improve understanding of the mechanisms of human brain functioning and neural development. In addition, these findings will be applied to elucidate the mechanisms of developmental disorders and to explore new medical therapies to treat them.

Keywords: maternal substance, brain, neuron–glia–vascular system, placenta, milk

1. Introduction

Every task performed by the mature nervous system — from the perception of sensory inputs and the control of motor output, to cognitive functions such as learning and memory — depends on precise interconnections between vast numbers of neurons. These connections are established during embryonic and early postnatal development. The development of the nervous system depends on the expression of particular genes at specific places and times during development. This spatio-temporal pattern of gene expression is regulated by both hard-wired molecular programs and epigenetic processes. The factors that control neural differentiation originate both from cellular sources within the embryo and from the external environment in forms such as secreted substances, nutrients, sensory stimuli, and social influences. The interaction of these intrinsic and extrinsic factors is critical for the normal development of neural networks (1).

Nutrients and hormones are necessary for healthy fetal growth and neural circuit formation (2). Because offspring depend entirely on the mother for the supply of nutrients during fetal and early postnatal development, the maternal nutrient and hormonal state during pregnancy/lactation is of utmost importance. However, a full understanding of the molecular basis of nutrients and bio-active agents necessary for neural development is currently lacking. Recent studies using animal models have demonstrated that maternally expressed substances (e.g., essential nutrients, hormones, growth factors, and trophic factors) are also transferred from mother to offspring via the placenta or breast milk (2–8). Some of these bio-active agents could influence the development of the fetal and neonatal brain and the subsequent...
expression and maintenance of higher brain functions. Conversely, during human pregnancy, the placenta and fetal membranes produce large amounts of corticotrophin-releasing hormone (CRH). It has been suggested that the high levels of CRH may be involved in the placental clock determining the onset of parturition (9). From these findings, we here propose the term “bio-communication” to describe these molecule-based biological conversations between mother and offspring (Fig. 1). We focus here on the role of the maternal substances that regulate neural development in offspring. Clarifying the regulatory mechanisms of “bio-communications” would contribute greatly to the understanding of neural development and brain function in humans. In this review, we summarize recent findings obtained primarily from animal models examining maternally expressed substances that regulate the neural development and brain function of offspring under normal and pathological conditions.

2. Maternal hormones and peptides regulating brain development in offspring

Recent studies using animals have demonstrated that maternally expressed bio-active agents, such as cytokines, peptides, and hormones, are transferred from the mother to the fetus via the placenta, affecting development. Here we review the physiological effects of maternal vasoactive intestinal peptide (VIP), ghrelin, and oxytocin (OXT) on the neural development of offspring.

There is increasing evidence that VIP regulates growth and development during the early post-implantation period of embryogenesis, the phase characterized by neural tube closure and the initiation of neurogenesis. In the mouse embryo, VIP stimulates the secretion of nerve growth factor, a well-recognized regulator of neuronal differentiation and survival. In addition, VIP regulates embryonic neural tube closure (10). Although VIP and its receptors are expressed early in mouse development, VIP gene expression in the embryo occurs later in embryogenesis. This suggests that VIP is maternally supplied in early embryonic development (3). VIP has been shown to cross the developing placenta, and maternal uterine tissues are a likely source of a peptide acting on embryonic VIP receptors, which regulates growth and development in the mouse embryo (11). In addition, a recent study has shown that mice treated with a VIP antagonist during the early embryonic period exhibited abnormal social behavior in adulthood (12).

Ghrelin, a gastrointestinal peptide, is the endogenous ligand for the growth hormone secretagogue receptor (GHS-R) and stimulates growth hormone (GH) secretion in the pituitary gland. By acting as a leptin antagonist, ghrelin regulates the synthesis and secretion of several neuropeptides in the hypothalamus that regulate food intake and energy balance (13). In addition to regulating the endocrine system, administration of ghrelin produces anxiolytic- and antidepressant-like responses (14). This suggests that ghrelin modulates neural circuit activity. The involvement of ghrelin in fetal development has recently been examined. The gene expression of GHS-R
was detected in the embryonic brain (4), and ghrelin treatment facilitates cell proliferation of neural progenitor cells from the rat fetal spinal cord in vitro (15). Chronic ghrelin treatment in pregnant rats was shown to cross the placenta to the fetus and increase the birth weight of newborn pups (4). Interestingly, when ghrelin was administered to pregnant mice, their offspring exhibited suppression of exploratory behaviors in adulthood (16). Reduced GHS-R and neuropeptide-Y expression in the hypothalamus were observed in these offspring, a change that persisted into adulthood (16). This finding suggests that prenatal ghrelin administration leads to long-lasting changes in neural circuits during postnatal development. Interestingly, ghrelin is produced and secreted by maternal breast cells (17). Although its functional role remains unclear, maternal ghrelin transferring via breast milk might play an important regulatory neuro-developmental role in suckling pups.

OXT, secreted from the posterior pituitary gland, is increased during parturition. Secretion of OXT is stimulated by uterine contractions that forcefully expel the fetus (5). In turn, OXT stimulates further contractions of the uterus. This uterine response is highly sensitive to OXT at the end of pregnancy. In addition, OXT induces a milk secretion in dams. These endocrinological and reproductive functions are essential for offspring survival. Moreover, it has been demonstrated that maternal OXT can cross the placenta (5). A recent study by Tyzio and colleagues described the physiological functions of maternal OXT on the fetal nervous system. This study demonstrated a novel role for maternal OXT within the rat brain as a neuroprotective agent that protects the fetal hippocampus from hypoxic or hypoglycemic insult. Maternal OXT was found to act as a transient switch of γ-aminobutyric acid (GABA) from excitatory to inhibitory activity in the fetal hippocampus at the time of birth (18). Because OXT synthesis within the supraoptic nucleus of the rat fetus has been reported to begin after birth (19), Tyzio et al.’s findings indicate that maternal OXT inhibits fetal neurons and increases their resistance to insult during delivery.

3. Maternal nutrition regulating brain development in offspring

3.1. Essential nutrients in brain development

Dietary deficiencies or imbalances of key nutrients at critical stages of development can have long-lasting and irreversible effects on brain development and neural function. The n-3 and n-6 polyunsaturated fatty acids are essential nutrients required for growth and normal neural functioning. These fatty acids cannot be synthesized de novo by mammalian cells. Therefore, these acids and their precursors must be derived entirely from the mother by placental transfer in order to be accumulated by the fetus. After birth, they must be provided by maternal milk (6). For example, n-3 fatty acid docosahexaenoic acid (DHA) is important because it is selectively accumulated in the membrane amino phospholipids of the retina and gray matter in the brain. Animal models have shown that a maternal n-3–deficient diet produces a DHA deficiency in the brain of offspring. Reduced accretion of DHA in the retina and brain during development leads to reductions in the size of neuronal cell bodies (20) and affects monoaminergic (dopaminergic and serotonergic) and cholinergic neurotransmission during development (21). Furthermore, spatial learning, spatial memory, and related tasks are also impaired in rodents fed an n-3 fatty acid–deficient diet during development (22).

Choline is another developmentally essential nutrient and is usually grouped within the vitamin B family of compounds. An adequate supply of vitamin B in the maternal diet during pregnancy is vital for normal fetal development. Choline acts as a precursor of phospholipid components of membranes, including those of neurons and glia. This essential nutrient may be crucial for the formation of circuits as precursor cells divide and grow, myelin is produced, and synapses are formed. In rodents, prenatal and postnatal dietary choline supplementations produce a long-lasting facilitation of spatial memory in offspring (7) and attenuate typical age-related declines in exploratory behavior (23). This long-term enhancement of cognitive function is likely to be accompanied by the facilitation of hippocampal long-term potentiation in adult rats (24).

3.2. Maternal overnutrition and brain development in offspring

Excess maternal dietary intake of certain nutrients also appears to influence brain development in offspring. There is evidence that high-calorie and high-fat dietary intakes lead to energy imbalances and can induce obesity in adults. Obesity is a global health issue, and its incidence is reaching epidemic proportions in some societies. In addition to the effects of maternal obesity on the metabolic functions and endocrine system in offspring, recent studies using animal models have demonstrated that offspring born from dams complicated by diet-induced obesity show abnormalities in neural circuit development. Maternal high-fat diets have been shown to induce obesity in offspring (25–27). In addition, maternal overnutrition has been found to alter hypothalamic leptin sensitivity (25) and increase the
expression of feeding-related peptides such as galanin, enkephalin, and dynorphin in the paraventricular nucleus in offspring (26). These offspring also exhibit an increased food intake and higher body weight after weaning (26). We have recently demonstrated that offspring from obese dams show hyperlipidemia and the peroxided lipid accumulation in the hippocampus during postnatal development (27). Moreover, we demonstrated a significant reduction of neurogenesis in these offspring during postnatal development. This finding suggests that maternal obesity impairs hippocampal progenitor cell viability and neuronal production in offspring because of metabolic and oxidative changes (27). However, changes in lipid and nutrient compositions in circulating blood and breast-milk from obese dams are not fully understood. Further studies will be required to understand changes caused by the transfer of maternal substances via the placenta and milk, and the effects of maternal obesity on the brains of developing offspring and their molecular mechanisms.

On the basis of these findings, we argue that maternal bio-active agents such as hormones, peptides, and nutrients play an important role in supporting and influencing the developing nervous system in offspring. Additionally, maternal metabolic conditions have long-lasting effects on both physical and cognitive functions that persist into adulthood. As well as investigating these substances, further studies will need to clarify the physiological roles of other maternal agents and their metabolites in brain development.


To understand the effects of maternal substances on neural development and function, it is important to know the regulatory mechanism by which these substances regulate neural networks at the cellular and molecular levels. The major cellular components of the brain are neurons, glia, and vascular cells. These three cell types form electrical and metabolic networks to enable neural circuit functioning. Neurons form neuronal networks, producing electrical activity that gives rise to brain functions, but the role of glia is less well understood. For much of the past century, glia were believed to have little influence on neuronal responses. Glia were thought to provide structural and metabolic support to neurons, but not to interact actively with them (28). Recent evidence, however, has demonstrated that bidirectional communication occurs between perisynaptic glia and neuronal elements at the synapse. Release of neurotransmitters from the pre-synaptic terminal not only stimulates the post-synaptic terminal but also activates the perisynaptic glia via glial neurotransmitter receptors (28, 29). Activated astrocytes (a subpopulation of glia) release transmitters and trophic factors that can directly stimulate the postsynaptic site either enhancing or depressing the further release of neurotransmitter from the pre-synaptic neuron (28). Several recent studies have investigated the role of glial cells in higher brain functions and the effects of maternal agents on neuron–glia interactions. For example, β-lactotensin (β-LT) is derived from bovine milk β-lactoglobulin and has a high binding affinity for neurotensin receptors subtype 2 (Ntsr2). Interestingly, Ntsr2 is dominantly expressed on astrocytes (30). Mice administered with β-LT have been shown to have enhanced memory consolidation, possibly due to effects on the dopaminergic system (31). These findings suggest that milk constituents may have effects on glial cells that are necessary for the expression of higher brain functions in suckling pups.

Vascular cells have recently emerged as important contributors to neural development. In addition to their continuous supply of oxygen and nutrients, vascular cells guide developing axons (32) and provide trophic support and differentiation signals to neural progenitor cells (33). However, there is currently little information regarding maternal bio-active agents involved in regulating angiogenesis and vascular functions in the fetal and neonatal brain. Furthermore, along with astrocytes, vascular cells contribute to the composition of the blood brain barrier. As such, it is important to understand how maternal substances are transported to the central nervous system from the blood circulation in order to affect neural circuitry. Further studies will be necessary to fully understand the effects of maternal substances on glial cells and the vascular system and subsequent interactions with neuronal cells in the developing fetal and neonatal brain.

5. Future perspectives

Neuronal activity is no longer seen as the sole mechanism affecting information processing in the brain. To elucidate the roles of “bio-communication” in the brain, it is important to know the actions of maternal substances not only on neurons, but also their surroundings. On the other hand, there is currently a dearth of information about possible bio-signals from offspring to mother. For example, while it has been found that fetal cells can enter maternal blood circulation during pregnancy and engraft certain maternal tissues (including brain tissue) in both mice and humans (34), it is unclear whether fetal molecules could likewise be transferred to the mother via the placenta. If this process does indeed occur, it may be a mechanism involved in
the endocrine system and emotional regulation in pregnant dams. The discovery of evidence-based biological relationships between mother and offspring would help us better understand the precise mechanisms of neural development and brain function (Fig. 1). Moreover, further studies are necessary to clarify whether deficiencies in “bio-communication” can lead to the onset of neurodegenerative or psychiatric disorders in animal models and humans. These findings could be applied to the elucidation of developmental disorders and the exploration of new medical therapies to treat them.

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