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Long-term alterations in neural and endocrine processes induced by motherhood in mammals

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ABSTRACT

This article is part of a Special Issue "Parental Care".

The reproductive experience of pregnancy, lactation and motherhood can significantly remodel the female's biological state, affecting endocrine, neuroendocrine, neural, and immunological processes. The brain, pituitary gland, liver, thymus, and mammary tissue are among the structures that are modified by reproductive experience. The present review that focuses on rodent research, but also includes pertinent studies in sheep and other species, identifies specific changes in these processes brought about by the biological states of pregnancy, parturition, and lactation and how the components of reproductive experience contribute to the remodeling of the maternal brain and organ systems. Findings indicate that prior parity alters key circulating hormone levels and neural receptor gene expression. Moreover, reproductive experience results in modifications in neural processes and glial support. The possible role of pregnancy-induced neurogenesis is considered in the context of neuroplasticity and behavior, and the effects of reproductive experience on maternal memory, i.e. the retention of maternal behavior, together with anxiety and learning are presented. Together, these sets of findings support the concept that the neural and biological state of the adult female is significantly and dramatically altered on a long-term basis by the experiences of parity and motherhood. Remodeling of the maternal brain and other biological systems is posited to help facilitate adaptations to environmental/ecological challenges as the female raises young and ages.

A myriad of developmental experiences forge the operations of the adult female brain. These experiences include the female's prenatal and postnatal environments, early life experiences, nutrition, puberty, pregnancy, lactation, and social interactions throughout her lifetime. Recent research primarily conducted in rodents and to a lesser extent in sheep, women and other mammals, has established that during adulthood the "reproductive experience" that comprises pregnancy, lactation and motherhood can profoundly affect her physiology and behavior on a long-term, if not permanent, basis. Changes brought about by pregnancy and lactation contribute to alterations in a number of neural and biological systems, including key neuroendocrine and endocrine processes. The present review focuses upon the specific long-term shifts in neural, endocrine, immune and behavioral processes that result from the reproductive experience that accompanies motherhood. In addition to examination of the neurobiology of motherhood following pregnancy and lactation, the consequences of maternal care itself, independent of pregnancy and lactation, are explored, and comparisons made between these processes in females undergoing single or multiple pregnancies and lactations with those of non-parous maternal and non-maternal females. When taken together, these examinations reveal that prior motherhood, especially following a pregnancy and lactational period, results in demonstrable long-term alterations in neuroanatomical, neurochemical, neuroendocrine, endocrine, immunological and behavioral systems that are adaptive to the adult female in promoting species propagation and survival.

Reproductive experience

Adult female mammals can undergo a range of physiological changes associated with their reproductive experiences. The term reproductive experience here is meant to include both the singular events of mating, pregnancy, parturition, and lactation as well as the combination of these events. Moreover, since females can give birth once or multiple times as well as not give birth, the term multiple reproductive experiences is designated for so-called multiparous females (see Table 1 for classification of reproductive histories).

The reproductive status of the female as it turns out can significantly impact both her physiological and neurobiological states as reflected by differences in hormonal, neurotransmitter, neurochemical, neuroanatomical and behavioral states. The present paper specifically examines the plasticity induced by motherhood and the changes associated with and produced by these various reproductive experiences (see Fig. 1).

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Table 1
Reproductive status of adult females.

Reproductive status	Description
Nulliparous	Never has given birth
Primigravid	First or initial pregnancy
Primiparous	Gave birth once/first birth
Multigravid	Multiple pregnancies
Multiparous	Gave birth multiple times (≥2)

Reproductive experience and endocrine functions

One of the first studies documenting long-term changes in hormone levels resulting from reproductive experience was reported in women (Musey et al., 1987). Circulating prolactin (PRL) levels were significantly lower during the follicular phase of the menstrual cycle in previously parous women up to 10 years following giving birth to a child. Similar reductions in blood androgens and estrogens were detected when hormone levels in previously parous women were compared with those of nulliparous, age-matched subjects (Musey et al., 1986, 1987). A similar pattern of reduced PRL blood concentrations was subsequently identified in pregnant rats when PRL levels were compared between rats undergoing a second pregnancy (gestation day 12) with those found during a first pregnancy (Bridges and Hammer, 1992). Examination of circulating PRL levels during the mating-induced diurnal and nocturnal PRL surges in primigravid and multigravid rats, likewise, found reductions in PRL levels during these surge periods (Bridges et al., 1993; see Fig. 2) and shifts in hypothalamic monoaminergic activity in the multigravid subjects (Sider et al., 2002).

Similar reductions in circulating PRL were also found when PRL levels were compared between rats that experienced a prior parity with those of age-matched, nulliparous females; and PRL levels were lower in cycling primiparous subjects on proestrus of the estrous cycle (Bridges & Byrnes, 2006) as well as on diestrus (Anderson et al., 2006). Moreover, the suckling stimulus provided by young which induces a characteristic increase in circulating PRL induces a smaller increase in plasma PRL in multiparous (2nd lactation) mother rats when compared with that induced by suckling in primiparous dams (Mann and Bridges, 1992). This experiential shift in endocrine responsivity, i.e. reduced PRL secretion, likely involves neuroendocrine factors, including dopamine and endogenous opioids, which regulate PRL release during lactation (Ben-Jonathan, 1985; Selmanoff and Gregerson, 1986). The physiological consequences of this overall dampening of PRL secretion may reflect a shift in endocrine efficiencies such that less hormone may be needed to stimulate endocrine responses, such as lactogenesis, corpora lutea maintenance, and perhaps the female's behavior. Evidence for a shift in PRL responsiveness is presented later in this discussion.

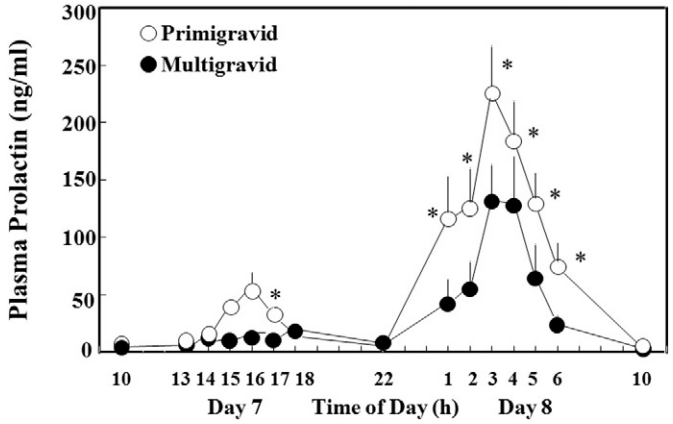

Fig. 2. Plasma PRL levels in primigravid (—○-) and multigravid (—●-) rats during a 24 h period starting at 1000 h on day 7 of pregnancy. Numbers on the abscissa refer to the time of day, e.g. 10 is 1000 h. * Significantly different from multigravid animals. Taken with permission from Pergamon Press Ltd., *Life Sciences* 53:439, 1993.

Prior reproductive experience also affects plasma estrogen levels during subsequent estrous cycles in rats; overall estradiol-17β are reduced in cycling primiparous compared with that of nulliparous controls (Bridges and Byrnes, 2006). The modest reduction in estrogen levels may partially account for the smaller estrogen-stimulated proestrus luteinizing hormone surge in previously parous rats (Bridges, unpublished data) and contribute to the prolongation of estrous cyclicity with reproductive experience over the female's lifetime by some undetermined mechanism (Matt et al., 1987; Hopwood et al. 1998). Estrogen-induced PRL sensitivity also shifts as a function of reproductive experience. Gonadectomized nulliparous rats were more sensitive than multiparous rats to lower doses of estradiol benzoate (EB), whereas multiparous subjects were more responsive to a high dose of EB

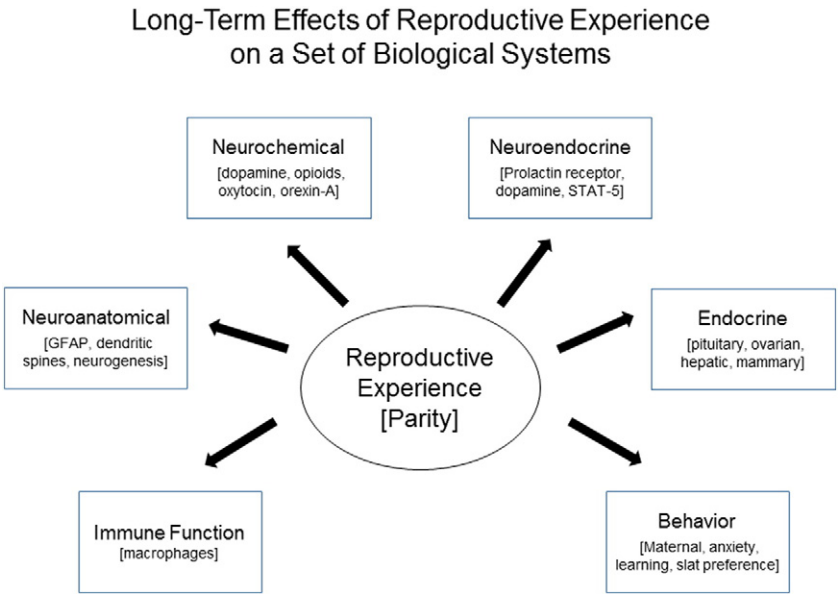

Fig. 1. Constellation of systems affected by the prior reproductive experiences of pregnancy, parturition and lactation.