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Review

Sex hormones and expression pattern of cytoskeletal proteins in the rat brain throughout pregnancy

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ABSTRACT

Pregnancy involves diverse changes in brain function that implicate a re-organization in neuronal cytoskeleton. In this physiological state, the brain is in contact with several hormones that it has never been exposed, as well as with very high levels of hormones that the brain has been in touch throughout life. Among the latter hormones are progesterone and estradiol which regulate several brain functions, including learning, memory, neuroprotection, and the display of sexual and maternal behavior. These functions involve changes in the structure and organization of neurons and glial cells that require the participation of cytoskeletal proteins whose expression and activity is regulated by estradiol and progesterone. We have found that the expression pattern of Microtubule Associated Protein 2, Tau, and Glial Fibrillary Acidic Protein changes in a tissue-specific manner in the brain of the rat throughout gestation and the start of lactation, suggesting that these proteins participate in the plastic changes observed in the brain during pregnancy.

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Contents

1. Introduction

In mammals the pregnant female provides an intrauterine environment suitable for fetus development. In the maternal brain, a large number of the physiological and behavioral changes that occur along pregnancy and in the postpartum period such as the increase in food intake and nesting construction depend on hormonal changes [1–4].

In pregnancy, the brain responds to hormones it has not been in contact with such as chorionic gonadotropin and placental lactogen [5,6], and to a very high levels of several hormones such as sex steroids. For example, in some strains, female rats are exposed to 45 pg/ml of estradiol between days 2 and 20 of pregnancy while they are exposed to 12 pg/ml on proestrus day [7]. Progesterone and its reduced metabolites can be synthesized in the brain in large amounts during pregnancy [8,9]. As a result of the increase and uninterrupted exposure to sex steroid hormones, the neuroendocrine regulation of many functions is significantly modified. The brain not only presents a different expression pattern of sex steroid receptors during pregnancy, but the metabolism of steroids is also modified [10]. The content of other hormones such as prolactin and oxytocin also changes during pregnancy, and they play a key role

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in the preparation of the neural substrates involved in the display of maternal behavior [11].

The brain presents a variety of morphophysiological changes during pregnancy including cell plasticity [7,12,13]. Initial experiments made by Diamond et al. showed a considerable increase in the thickness of the cortex during pregnancy, demonstrating that hormones–brain interaction during a long period of time such as pregnancy affects neuronal morphology [14]. Similar results have been found in late pregnant rats whose neurons soma from the medial preoptic area are bigger as compared with those from ovariectomized animals [15]. These data suggest that estradiol and progesterone play an important role in brain function during pregnancy that is associated to the expression of several behaviors, including the onset of maternal behavior [16].

In spatial memory tests, the performance of pregnant rats is better than that of non-pregnant ones [13,17]. Moreover, anxiety and fear are diminished during pregnancy. The levels of estradiol, progesterone and their metabolites are markedly higher in pregnant rats [7,8,18]. These high hormonal levels have been associated to the change in behavior that occurs along pregnancy such as those related with maternal behavior [19,20].

It has been demonstrated that in the CA1 field of the rodent hippocampus there is an increase in neurogenesis, cell proliferation, and the density of dendritic spines throughout pregnancy [15,17,21–23]. These plastic changes involve cytoskeletal reorganization. This review is focused on the expression pattern of three proteins involved in cytoskeletal organization of neurons and glial cells: Microtubule associated protein 2 (MAP2), Tau and Glial fibrillary acidic protein (GFAP) during pregnancy, and its relation with sex steroid hormones profile.

2. Sex steroids during pregnancy

Pregnancy is characterized by a progressive incrementing estradiol and progesterone levels, both prepare the neural circuit related to the display of maternal behavior [24]. In the rat, estradiol levels progressively increase during pregnancy reaching a peak before parturition, while those of progesterone rapidly increase after mating, reaching a first peak on day 6 of gestation, which is maintained until day 12; after then there is maximum on day 14, continuing until day 20 of pregnancy. Progesterone levels suddenly diminish near term, let parturition to occur and maternal behavior to be expressed [8].

Changes in estradiol and progesterone intracellular receptors (ER and PR, respectively) have also been reported in the brain during pregnancy. Two main subtypes of ER: ERα and ERβ as well as two PR isoforms, PR-A and PR-B, that exhibited different function and regulation have been reported [25–31].

ER binding changes in several brain regions during rat pregnancy [32]. For example, in the preoptic area of the rat, estrogen binding increases between days 8 and 16 of pregnancy, staying high on day 22 of parturition [27,33,34]. In the ventromedial nucleus, estrogen binding increases in early pregnancy but it is reduced on day 16, and rises on day 22 [34]. In the amygdala, estrogen binding dramatically increases during pregnancy (over 500%) [34]. On days 16 and 22 of pregnancy, preoptic area expressed a higher number of ER-positive cells as compared with day 8 or postpartum day 1. In the ventromedial hypothalamus, ER immunoreactivity per cell was higher on day 22 of pregnancy compared with day 16 and the first postpartum day [34]. Changes in ER expression at critical times in the preoptic area and the ventromedial nucleus suggest a key role of this receptor in maternal behavior.

PR has been detected in the forebrain of the rat during pregnancy using immunocytochemical procedures. It was found that the number of PR-positive cells was low in several hypothalamic nuclei on day 3, increasing later on days 15 and 21 of gestation [35].

Progesterone is rapidly metabolized in the brain to ring A-reduced progestin such as allopregnanolone (5α-pregnan-3α-ol-20-one) by the actions of 5α-reductase and 3α-hydroxysteroid dehydrogenase. During late pregnancy, the expression and activity of these enzymes are increased in several brain regions [10]. All these changes in sex steroids levels and the expression of their receptors during pregnancy have been related to cytoskeletal remodelation involved in brain plasticity in this physiological state.

3. MAP

Microtubule-associated proteins (MAPs) play a key role in the extension of neurites, axonal transport, neuronal plasticity and dendrite stability [36–39]. MAPs regulate the formation of microtubules, determining neuronal shape and size of neuronal processes. MAP2 can also bind to actin and modify microfilament stability in dendritic spines [40–42].

In the adult brain two proteins of high molecular weight (280 kDa), MAP2a and MAP2b, have been reported in dendrites and neuronal soma where they are mainly associated with microtubules [43,44] as well as with actin fibers in dendritic spines and postsynaptic terminals [41,42]. MAP2 has an important role in the regulation of dendritic outgrowth and synaptogenesis [45,46]. Reyna-Neyra et al., have demonstrated that estradiol and progesterone augment MAP2 expression in the hippocampus of ovariectomized rats [47,48]. Furthermore, in the rat, estradiol increases dendritic growth in mediobasal hypothalamic neurons, and the number of spines as well as that of dendritic synapses in the ventromedial nucleus [49,50]. This may contribute to the increase in dendritic spine density observed both on proestrus day and in hippocampal cell cultures after steroids treatment [51,52].

We have evaluated the expression of MAP2 in the hippocampus and the preoptic area throughout rat gestation and the beginning of lactation. In the hippocampus of pregnant rats the content of MAP2 decreased during pregnancy and in day 2 of lactation (Table 1). On the other hand, in preoptic area MAP2 content did not significantly change during pregnancy, however, it decreased on the beginning of lactation (Table 1). The differences in MAP2 protein content between hippocampus and preoptic area during pregnancy suggest that tissue-specific factors are involved in the regulation of MAP2 expression. Changes in MAP2 expression could be associated to the participation of different brain regions in the behavioral patterns observed throughout pregnancy.

4. Tau

Tau is another protein associated to microtubules that belongs to a family of proteins (45–65 kDa) mainly located in axons whose hyperphosphorylated forms have been related with several neurodegenerative disorders such as Alzheimer's disease [53]. The role of Tau in microtubules polymerization is driven by phosphorylation/dephosphorylation cycles. Thus, Tau phosphorylation at specific sites allows microtubules depolymerization, while Tau dephosphorylation promotes their stabilization [54,55]. Estradiol

Table 1
Changes in MAP2 content in the hippocampus and the preoptic area of the rat during pregnancy and on day 2 of lactation.

Days	G2	G14	G18	G21	L2
Hippocampus	100 ± 2	116 ± 4*	82 ± 9*	69 ± 3*	65 ± 11*
Preoptic area	100 ± 2	96 ± 8	71 ± 16	89 ± 16	54 ± 14*

Days 2, 14, 18, and 21 of gestation (G2, G14, G18, G21, respectively), and day 2 of lactation (L2). Data show the percentage change in protein content of MAP2 as compared with day 2 of gestation. Results are expressed as mean ± S.E.M. $n = 4$.

* $P < 0.05$ vs G2.