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Research Report

Progesterone receptor expression in the brain of the socially monogamous and paternal male prairie vole

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ABSTRACT

Differences in the social organization and behavior of male mammals are attributable to species differences in neurochemistry, including differential expression of steroid hormone receptors. However, the distribution of progestin receptors (PR) in a socially monogamous and spontaneously parental male rodent has never been examined. Here we determined if PR exists and is regulated by testicular hormones in forebrain sites traditionally influencing socioreproductive behaviors in male prairie voles (*Microtus ochrogaster*). We hypothesized that PR expression in male prairie voles would differ from that described in other male rodents because PR activity inhibits parental behaviors and social memory in laboratory mice and rats. Adult male prairie voles received a sham surgery, were gonadectomized, or were gonadectomized and implanted with a testosterone-filled capsule. PR immunoreactivity (PRir) was measured four weeks later in areas of the hypothalamus and extended amygdala. A group of gonadally intact female prairie voles was included to reveal possible sex differences. We found considerable PRir in all sites examined. Castration reduced PRir in males' medial preoptic nucleus, anteroventral periventricular nucleus, ventromedial hypothalamus, and posterodorsal medial amygdala, and it was maintained in these sites by testosterone. This is the first study to examine PR expression in brain sites involved in socioreproductive behaviors in a socially monogamous and spontaneously paternal male rodent. Our results mostly reveal cross-species conservation in the distribution and hormone sensitivity of PR expression. Because PR interferes with aspects of sociality in other male rodents, PR may eventually be found to have different neurobiological actions in male prairie voles.

1. Introduction

Male mammals differ tremendously in their social organization and the behaviors they display within their species-specific contexts (Clutton-Brock, 2009). Laboratory studies examining the neurobiology underlying differences in social organization and behavior have often compared socially monogamous and biparental male rodents with those that are socially

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non-monogamous and uniparental (i.e., the mother is the only caregiver) to better understand the proximate and ultimate causes of their markedly different behavioral repertoires. For example, male laboratory rats, most male inbred mice, and males of some species of voles are polygamous and also do not typically display caregiving behaviors. Conversely, other male rodents including prairie voles (*Microtus ochrogaster*) form lifelong pair bonds after mating and are highly parental even without sexual experience (Young et al., 2011). Studies examining neurobiological correlates of these species differences in sociality have implicated numerous peptide systems in the forebrain. Male prairie voles have 3–6-fold greater oxytocin receptor expression in the nucleus accumbens and bed nucleus of the stria terminalis (BST) compared to polygamous and non-parental male voles. Prairie voles also differ from polygamous voles in their vasopressin V1a receptor expression in the BST, ventral pallidum and olfactory bulb (Insel and Shapiro, 1992; Insel et al., 1994), and in their corticotropin-releasing hormone (CRH) receptor expression in many areas of the brain (Lim et al., 2005).

In addition to neuropeptides, expression of forebrain steroid hormone receptors differs between paternal and monogamous rodents and uniparental and polygamous ones. Cushing and colleagues have shown that the paternal and socially monogamous pine vole (*Microtus pinetorum*) has lower estrogen receptor isoform alpha (ERα) expression in the medial amygdala and BST compared to the polygamous and non-parental montane vole (*Microtus montanus*) (Cushing and Wynne-Edwards, 2006). They also found that the highly parental male Djungarian hamster (*Phodopus sungorus*) has lower ERα expression in the BST than does the less parental male Siberian hamster (Cushing and Wynne-Edwards, 2006). Even within prairie voles, more social members of the species have lower ERα expression in the medial preoptic area, ventromedial hypothalamus, and BST compared to less social individuals (Cushing et al., 2004). A relationship between sociality and androgen receptor expression in these brain sites has not been found, though (Cushing et al., 2004). The functional significance of these differences in ERα expression is demonstrated by the reduced sociality in male prairie voles with viral vector-mediated overexpression of ERα in the medial amygdala or BST (Cushing et al., 2008; Lei et al., 2010).

The neural network necessary for parental and other social behaviors in rodents not only contains high densities of estrogen and androgen receptors (Koch and Ehret, 1989; Li et al., 1997; Pfaff and Keiner, 1973; Simerly et al., 1990), but is also exquisitely responsive to progesterone. Progesterone mediates many of its neurobehavioral functions by acting on two isoforms of a classic nuclear receptor, PRA and PRB (Wagner, 2006; Mani et al., 2006), that differ in their ratio depending on the brain site and hormone milieu (Carrillo-Martínez et al., 2011). PR relevance for social behavior in male rodents is readily demonstrated by progesterone receptor knockout mice (PRKOs), which exhibit aberrations in most social behaviors examined including responses to pups and copulation (Lydon et al., 1995; Phelps et al., 1998; Schneider et al., 2003).

PR expression within the rodent brain, particularly within the hypothalamus/preoptic area, is influenced by gonadal hormones. Indeed, numerous investigations have demonstrated that estradiol or testosterone treatment increases brain PR binding, PR mRNA levels, and PR protein expression (Blaustein and Turcotte, 1989; Blaustein et al., 1980, 1988; Brown et al., 1987, 1996; Etgen, 1985; Lauber et al., 1991; Moguilewsky and Raynaud, 1979; Scott et al., 2002; Shughrue et al., 1997; Simerly et al., 1996; Warembourg et al., 1989). What is most striking about this hormone-mediated regulation of PR expression in the brain is that it is evolutionarily conserved and present in many non-mammalian species including whiptail lizards (Godwin and Crews, 1999), chickens (Gasc and Baulieu, 1988), and frogs (Roy et al., 1986).

In the present study we investigated whether PR expression in neural sites traditionally involved in mammalian social behaviors differs between male prairie voles and what has typically been reported in non-parental, polygamous, and less gregarious male rodents (including laboratory rats and mice). This was of interest because the inhibition of parenting in non-parental male mice requires the presence of PR (Schneider et al., 2003), so in prairie voles one may expect a paucity of PR in brain sites such as the preoptic area (POA) and bed nucleus of the stria terminalis (BST) that promote parental behaviors (Numan and Insel, 2003). Additionally, we were interested in whether the gonadal hormone upregulation of PR seen in polygamous rodents would also exist in prairie voles. As noted above, the upregulation of preoptic and hypothalamic PR by steroid hormones is thought to be an evolutionarily conserved phenomenon, but given the spontaneous paternal behavior of male prairie voles, it could be counterproductive to have PR in their POA upregulated by testicular hormones. To accomplish these goals, we examined PR immunoreactivity in select regions of the male prairie vole forebrain in animals that were gonadally intact, castrated, or castrated and subcutaneously implanted with a testosterone-filled capsule. A group of gonadally intact virgin female prairie voles, which are induced ovulators with very low circulating ovarian hormones in the absence of male cues (Carter et al., 1989), were also examined.

2. Results

PRir was present in all six brain sites analyzed in all groups of voles (Fig. 1). In the medial preoptic nucleus (MPN), Sham males had very high levels of PRir that were reduced by castration and maintained by testosterone ($F(3,23)=9.00$, $p<0.001$; Figs. 2 and 3). Females had relatively low PRir in the MPN, similar to castrated males. In the anteroventral periventricular nucleus (AVPV), high levels of PRir were found in Sham males, GDX+T males, and females. PRir in the AVPV of GDX males was significantly lower than all of these groups ($F(3,20)=5.358$, $p<0.009$; Fig. 3).

In the principal nucleus of the bed nucleus of the stria terminalis (pBST), GDX+T males had significantly more PRir than did GDX males ($H=11.75$ $p<0.008$; Fig. 4); no other group comparisons in this site were statistically significant. In the posterodorsal medial amygdala (MeApd) the pattern of differences among groups was similar to that found in the MPN—very high PRir in Sham and GDX+T males and significantly lower PRir in GDX males and females ($F(3,20)=6.22$, $p<0.005$; Fig. 4).