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Medroxyprogesterone acetate acutely facilitates and sequentially inhibits sexual behavior in female rats

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Abstract

Medroxyprogesterone acetate (MPA), a synthetic progestin commonly used in contraception and hormone replacement therapy, appears to inhibit libido in women, but little is known about the mechanisms through which it may exert this effect. We compared the acute and sequential actions of MPA and natural progesterone (P4) on sexual behavior in female rats to test the hypothesis that MPA inhibits sexual behavior, at least in part, by acting as a potent progesterone receptor (PR) agonist. Ovariectomized females were placed in one of three dose groups (high, mid, or low), and each subject was tested under three different conditions (MPA, P4, and vehicle). The order of progestin treatment was balanced among subjects, and within each dose group equimolar quantities of MPA and P4 were administered. During each trial, females were injected with estradiol benzoate (EB, 4 μg) followed by one of three progestin treatments (MPA, P4, or vehicle) at +44 h, and behavioral testing at +48 h. On the next day, all females were given a standard 500-μg injection of P4 at +68 h and were tested again for sexual behavior at +72 h. On the first day of behavioral testing, both MPA and P4 induced a pronounced rise in receptive and proceptive behavior at the mid and high doses, but at the lowest dose MPA had a much greater effect in comparison to P4. On the second day of behavioral testing, MPA attenuated the expression of proceptive and receptive behavior at both the mid and high doses, whereas P4 only attenuated the expression of lordosis and only did so at the highest dose. These findings illustrate that MPA and P4 have a similar impact on sexual behavior in female rats and suggest that the inhibitory effects of MPA may be attributable, at least in part, to its potent effects at the progesterone receptor.

Keywords: Medroxyprogesterone; Progesterone; Progesterone receptor; Lordosis; Proceptivity; Hormone replacement

Introduction

Medroxyprogesterone acetate (MPA) commonly is used in contraception and hormone replacement therapy. Like other progestins, MPA counters the proliferative effects of estrogen treatment in the uterus and protects against endometrial hyperplasia (Sitruk-Ware, 2000; The Writing Group for the PEPI Trial, 1996). Similarly, MPA has been shown to inhibit gonadotropin release and may prevent ovulation (Bagis et al., 2002; Bassol et al., 1984; Fiad et al., 1996; Saaresranta et al., 2002). The effective use of MPA in therapies requiring the induction of progestin effects is related not only to its high oral activity, but also to its pronounced binding and activational effects at progesterone receptors (PRs) (Dijkema et al., 1998; Kuhl, 1990; Levin et al., 1990; Pridjian et al., 1987; Rebar and Zeserson, 1991; Schoonen et al., 1998; Selman et al., 1996).

While MPA effectively controls endometrial hyperplasia and inhibits gonadotropin release, it also appears to have profound inhibitory effects on sexual motivation and behavior. Many woman using MPA for hormonal therapies complain of reduced libido (for a review, see Kaunitz,

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2001), and in ovariectomized macaques we have shown that although P4 diminishes the facilitatory effects of estradiol on sexual behavior, MPA completely antagonizes estradiol's effects and reduces sexual initiation rates to baseline levels observed under placebo treatment (Pazol et al., 2004).

Potentially the more profound inhibitory effects of MPA as compared to P4 can be attributed to its actions as a potent PR agonist. Indeed, in male macaques it has been shown that both [^{3}H]MPA and [^{3}H]P4 accumulate in their unchanged form in the cell nuclei of the hypothalamus and preoptic area (Bonsall et al., 1990; Rees et al., 1986). Moreover, comparative studies have shown that in relation to P4, MPA has an equal to greater binding affinity and biological potency at PRs (Kuhl, 1990; Rebar and Zeserson, 1991). However, most studies comparing the effects of MPA and P4 have been conducted on peripheral tissues of the reproductive system (e.g., Di Carlo et al., 1984; Pridjian et al., 1987; Schoonen et al., 1998); because the relative strength of progestins can differ across organ systems (Schoonen et al., 1998), the results of these studies cannot be extrapolated with confidence to predict MPA's effects at central PRs.

While MPA may exert its effects by acting as a potent PR agonist, it also has the potential to inhibit sexual behavior by acting through a number of neurochemical systems in ways that P4 does not. In contrast to the specificity of P4 for PRs, MPA also shows substantial binding and activational effects at androgen and glucocorticoid receptors (Bamberger et al., 1999; Bardin et al., 1983; Hackenberg et al., 1993; Hellman et al., 1976; Kontula et al., 1983; Labrie et al., 1987; Selman et al., 1997). In addition, although P4 is endogenously reduced to a number of neuroactive metabolites, MPA acts as a competitive inhibitor for the enzymes needed for this conversion while failing to show similar neural activity in its parallel reduced form (Jarrell, 1984; Lee et al., 1999; Penning et al., 1985).

Determining whether MPA's inhibitory effects are attributable to its actions at PRs is difficult in primates because P4's effects on sexual behavior are not well understood in these species. Numerous studies conducted in naturalistic groups, or other settings which allow females to control the timing of mating, have shown that rates of sexual activity fall during the luteal phase of the menstrual cycle when P4 levels are high, and that serum P4 levels correlate negatively with the expression of sexual behavior (Bonsall et al., 1978; Carosi et al., 1999; Czaja, 1975; Gordon, 1981; Michael and Bonsall, 1977; Pomerantz and Goy, 1983; Wallen et al., 1984; Wilson et al., 1982b; Zehr et al., 1998). Similarly, in a number of studies, administration of exogenous P4 has offset the facilitatory effects of estradiol (Kendrick and Dixson, 1985; Lipschitz, 1997; Michael et al., 1968). Nonetheless, in one study, P4 induced a pronounced increase in female sexual initiation rates (Baum et al., 1976, 1977), and in cycling females copulation rates are highest at the point in their menstrual cycle when P4 levels first rise (Wilson et al., 1982b). Thus, it has been suggested that P4 may initially synergize with estradiol to facilitate sexual behavior, or that it may facilitate sexual behavior when it is present at very low concentrations (Michael and Bonsall, 1979; Wilson et al., 1982a,b).

In contrast to the little that is known for primates, in rodents it has been well documented that P4 acts synergistically with estradiol to induce both receptive and proceptive behavior (Blaustein and Erskine, 2002). Estradiol priming can induce low levels of receptivity, but subsequent P4 treatment enhances this response and is necessary for the induction of proceptive behavior (Brandling-Bennett et al., 1999; Erskine, 1989; Fadem et al., 1979; Gilman and Hitt, 1978; Hardy and DeBold, 1971; Tennent et al., 1980; Whalen, 1974). The importance of P4's actions at PRs is suggested by the temporal correlation between the rise in estradiol induced hypothalamic PRs and the onset of behavioral responsiveness to P4 (McGinnis et al., 1981; Moguilewsky and Raynaud, 1979). Moreover, a number of studies have shown that PR antagonists or antisense oligonucleotides prevent the expression of P4-mediated receptive and proceptive behavior (Brown and Blaustein, 1984; Etgen and Barfield, 1986; Frye et al., 2000; Ogawa et al., 1994; Pollio et al., 1993). However, in addition to facilitating the expression of sexual behavior, P4 reduces the availability of hypothalamic PRs and subsequently induces a refractory period during which females are unresponsive to further P4 treatment (Ahdieh et al., 1983; Blaustein, 1982; Blaustein and Wade, 1977; Hansen and Sodersten, 1979; Marrone et al., 1977; Nadler, 1970; Parsons et al., 1981; Powers and Moreines, 1976; Wallen et al., 1975; Zucker, 1968). Hence, while P4 initially facilitates sexual behavior in female rodents, prolonged exposure has an inhibitory effect.

In this paper we use the well-established, PR-mediated biphasic effects of P4 on sexual behavior in rodents to evaluate the hypothesis that MPA inhibits female sexual behavior, at least in part, by acting as a potent PR agonist within relevant neurochemical systems. Accordingly, we predict that lower doses of MPA as compared to P4 will be needed initially to induce sexual behavior in estrogen-primed female rats. We further predict that lower doses of MPA as compared to P4 will be needed to induce a refractory period during which females are no longer responsive to a standard dose of P4.

Methods

Subjects and housing

Study subjects were female Long–Evans rats (N = 20) that had been ovariectomized prior to shipment (Harlan, Indianapolis, IN). All subjects were singly housed and maintained on a 12:12-h reversed light/dark cycle. Retired male breeders (N = 10, Harlan, Indianapolis, IN) were used in testing for sexual behavior. The males were also singly housed and kept in a separate cubicle from the females.