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Research Report

Organizational manipulation of gonadal hormones and systemic morphine analgesia in female rats: Effects of adult ovariectomy and estradiol replacement

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Abstract

Previous research has indicated the importance of sex in mediating the larger magnitude of μ-opioid receptor agonist-induced analgesia in male relative to female rodents. Whereas manipulations involving the adult activational effects of gonadal hormones minimally alter these analgesic sex differences, manipulations involving neonatal organizational effects of gonadal hormones have previously been shown to profoundly affect morphine analgesia. Thus, adult male rats neonatally castrated on the first day after birth displayed reductions in morphine analgesia relative to sham-operated males, and adult female rats neonatally treated with testosterone propionate on the first day after birth displayed enhancements in morphine analgesia relative to vehicle-treated females. Because neonatal androgenization in female rats produces an anovulatory syndrome that could change their adult hormonal milieu, the present study examined whether adult ovariectomy altered the magnitude of systemic morphine analgesia (1–5 mg/kg) in neonatal androgenized female rats relative to neonatal vehicle-treated female rats as well as gonadal steroid hormone replacement with estradiol benzoate. Intact male rats displayed significantly greater magnitudes and potencies (2- to 2.3-fold leftward shift) of systemic morphine analgesia than female rats treated neonatally with either vehicle (1–5 mg/kg) or testosterone (1.7–5 mg/kg). In turn, neonatal androgenized female rats displayed significantly greater magnitudes of systemic morphine (1, 5 mg/kg) analgesia than vehicle-treated female rats accompanied by a smaller 20% leftward shift in potency. Adult ovariectomy minimally affected morphine analgesia in neonatal vehicle-treated females, while significantly reducing the magnitude (1 mg/kg), but not the potency of morphine analgesia in neonatal androgenized female rats. Estradiol replacement therapy significantly increased the magnitude of morphine analgesia in both groups at some doses, but only changed the potency (20–30%) in females treated neonatally with vehicle. Taken together, these data suggest a limited organizational-activational gonadal hormone interaction in the mediation of systemic morphine analgesia in female rats.

Theme: Sensory systems
Topic: Pain modulation: pharmacology

Keywords: Testosterone propionate; Estradiol benzoate; Ovariectomy; Tail-flick latency

1. Introduction

Potent sex differences in analgesic processes have been described (e.g., see reviews: [8,19]), particularly in the magnitude of μ-opioid receptor agonist-induced analgesia with female rodents displaying significantly smaller responses than male rodents following systemic, ventricular or intracerebral injections (e.g., [2,3,9,10,23,25,28,29]). Genotype influences sex differences in morphine analgesia such that AKR/J, C57BL/6J and SWR/J murine strains show greater morphine analgesia in males, and the CBA/J strain shows greater morphine analgesia in females (e.g., [27,34]).

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Moreover, sex differences in morphine analgesia are most potent in Wistar and Lewis rat strains, moderate in Sprague–Dawley and F344 strains, and least in Long Evans, Brown Norway and Holtzman strains [46,47]. Age and sex interact in mediating these effects given significant age-related increases in female rats and decreases in male rats in the ED_{50} of morphine analgesia [21]. Pharmacokinetic factors fail to explain the sex differences in the greater morphine analgesia in male relative to female rats [11,12]. It appears that more potent μ agonists (e.g., etorphine, DAMGO, β-endorphin) produce more pronounced analgesic sex differences than less potent μ agonists [12,16,17,26,29,35,45]. Moreover, some (DPDPE, deltorphin), but not all δ agonists, and some (U50488H), but not all κ agonists produced greater analgesic responses in male rats [5–7,17,24,26,38].

Whereas gonadectomy in adult male and female animals reduced analgesic sex differences elicited by both opioid-mediated and nonopioid-mediated swim stressors (e.g., see review: [8,19]), these manipulations minimally altered the magnitude or the potency of either morphine or DAMGO analgesia relative to intact males and females [1,4,11,13,21,22,25,26,28]. This suggests that the classically-described activational effects of gonadal hormones (e.g., [40]) may not be pivotal in the mediation of these analgesic responses, although adult gonadectomy does affect μ agonist-mediated analgesia when using less potent agonists [45]. Morphine analgesia was more potent in female rats during proestrus and diestrus than during estrus, but was less potent in gonadectomized females receiving estradiol, progesterone or testosterone [25,44]. In contrast, classically described organizational effects of gonadal hormones (e.g., [40]) may be important in the mediation of these responses given that morphine analgesia elicited from either the ventro-lateral periaqueductal gray (vlPAG: [30]) or following systemic administration [13] was profoundly affected by neonatal gonadectomy. Thus, adult male rats neonatally castrated on Day 1 after birth displayed magnitudes and potencies of either intracerebral or systemic morphine-induced analgesia that were significantly lower than sham-operated males, but similar to that of neonatal vehicle-treated females tested during the estrus phase. Correspondingly, adult female rats neonatally treated with testosterone propionate (TP) on Day 1 after birth displayed magnitudes and potencies of either intracerebral or systemic morphine-induced analgesia that were significantly higher than neonatal vehicle-treated females tested during the estrus phase, but similar to that of sham-operated males. Thus, these organizational manipulations may produce important changes in brain circuitry that influence gonadal hormone modulation of supraspinal (e.g., see reviews: [8,19,39]) and spinal [31,32] sites relevant to analgesic processes.

Although these neonatal gonadectomy effects suggest a potential pure organizational role of gonadal hormones in mediating sex differences in morphine analgesia, this is not certain because neonatal androgenization in female rats produces an anovulatory syndrome that could change the adult hormonal milieu in female rats (see review: [39]). Several instances of such an interaction include the ability of adult ovariectomy to increase TP-induced aggressive behaviors in female mice treated neonatally with TP, but not vehicle [15] and to reverse the reductions in physiologically-elicited corticosterone parameters in female rats treated neonatally with TP [42]. Combinations of neonatal TP and adult ovariectomy reversed the sex difference observed for the constitutive expression of preprocholecystokinin mRNA in the medial amygdala and bed nucleus of the stria terminalis with males showing higher expression than females [33]. However, adult ovariectomy failed to alter the increased dendritic branching in cortical pyramidal cells observed in female rats treated neonatally with TP [43]. More detailed differentiation of the various causal routes of neonatal androgenization influences would also require exogenous steroid hormone treatment especially in the absence of female gonads. Estrogen alone or in combination with progesterone has had mixed facilitatory and inhibitory effects upon opioid-induced analgesia per se [4,14,35–37,41], but exogenous gonadal hormone steroid replacement has not been tested for analgesic responses in female animals exposed to neonatal androgenization and/or adult gonadectomy. Therefore, the present study first examined whether adult ovariectomy altered the adult potency and magnitude of systemic morphine analgesia in neonatal androgenized female rats relative to female rats neonatally treated with vehicle. The present study then examined whether gonadal hormone steroid replacement with estradiol benzoate (EB) in neonatal androgenized and neonatal vehicle-treated females altered any adult ovariectomy-induced effects upon systemic morphine analgesia. To determine whether sex differences were observed, an additional group of male rats were tested as well. Both full dose–response (0, 1, 1.7, 2.5 and 5 mg/kg, sc) and time–response (30, 60, 90 and 120 min) functions of systemic morphine analgesia were assessed using the tail-flick test in all groups.

2. Methods and materials

2.1. Subjects and treatments

All procedures were approved by the Queens College Institutional Animal Care and Use Committee. Timed pregnant female albino Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) were delivered at approximately 12–14 days into gestation, and were subsequently housed individually in polyethylene cages with animal bedding in the Queens College Vivarium. The females, maintained on a 12-h light:12-h dark cycle with Purina rat chow and water available ad libitum, were monitored for delivery between days 20 and 22 of gestation. With the date of birth denoted as day 0, female