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Review

Sex steroids as pheromones in mammals: The exceptional role of estradiol

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ABSTRACT

This article is part of a Special Issue (Chemosignals and Reproduction).

Whether from endogenous or exogenous sources, 17β-estradiol (E_2) has very powerful influences over mammalian female reproductive physiology and behavior. Given its highly lipophilic nature and low molecular mass, E_2 readily enters excretions and can be absorbed from exogenous sources via nasal, cutaneous, and other modes of exposure. Indeed, systemic injection of tritiated estradiol (^{3}H-E_2) into a male mouse or bat has been shown to produce significant levels of radioactivity in the reproductive tissues and brain of cohabiting female conspecifics. Bioactive E_2 and other steroids are naturally found in male mouse urine and other excretions, and males actively direct their urine at proximate females. Very low doses of E_2 can mimic the Bruce effect (disruption of peri-implantation pregnancy by novel males), the Vandenbergh effect (early reproductive maturation induced by novel males), and male-induced estrus and ovulation. Males' capacities to induce the Bruce and Vandenbergh effects can both be diminished by manipulations that reduce their urinary E_2. Uterine dynamics during the Bruce and Vandenbergh effects are consistent with the actions of E_2. Collectively, these data demonstrate a critical role of male-sourced E_2 in these major mammalian pheromonal effects.

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Introduction

Estrogens exert many powerful roles in mammalian female reproductive processes. Conventionally, estrogens and other steroids are understood to originate and act within the same individual. I will review evidence demonstrating that estrogens can transfer between cohabiting individuals, arriving directly at sites in the reproductive tract, brain, and other tissues of the receiving individual. I will then review evidence that estrogen actions are critical for some of the best known mammalian pheromonal effects. The focus will be on female reproductive processes, as most major mammalian pheromonal processes, including the Bruce, Vandenbergh, and Whitten effects, involve male actions affecting females, while others such as the Lee–Boot effect involve females affecting each other. All of these are potentially explained, at least in part, by steroid transfer among individuals. I will use the term "pheromone" to refer to mammalian phenomena that have traditionally been associated with the term, all of which involve impacts of chemicals excreted by one individual that have some bearing on the behavior and/or physiology of certain proximate conspecifics. The connotations of this term have evolved as science has progressed, and may not be as precise as those in the original usages (see reviews by McClintock, 2002; Petrulis, 2013).

Roles of estrogens in mammalian female reproduction

Estrogens are the smallest steroids, with only 18 carbons. The best known estrogens are estrone (E_1), 17β-estradiol (E_2), and estriol (E_3). They are last in the biosynthetic chain that progressively strips down steroid precursors to more potent molecules of lower mass in the gonads and adrenal cortex. Their immediate 19-carbon precursors are androgens, which are converted to estrogens by the aromatase enzyme (reviewed in Simpson et al., 2002). Estrogens are highly lipophilic and can be converted from one to another. They are not metabolically degraded, but they can be conjugated by enzymes, especially in the liver, which involves converting them to larger, more water soluble forms that are biologically inert and readily excreted. In binding to estrogen receptors (ER), E_2 is substantially more potent than E_1 or E_3 (Kuiper et al., 1997). Conventional genomic ER are intracellular proteins that alter gene transcription, and are found in two forms (ERα and ERβ), while recent evidence also indicates the existence of extracellular, membrane-bound ER (reviewed in Levin, 2009). There are heavy concentrations of ER in the uterus and ovaries of females (Couse et al., 1997; Hiroi et al., 1999; Kuiper et al., 1997). In the brain, there are concentrations of ER in some limbic structures and the hypothalamus, particularly the ventromedial and preoptic areas (Pfaff, 1980; Simerly et al., 1990). Increasingly, evidence indicates that ER occur in diverse locations, including some presence in the heart, kidneys, lungs, olfactory bulbs, and cerebral cortex, among other tissues (Couse et al., 1997; Kuiper et al., 1997).

Estrogens play many critical roles in mammalian female development, fertility, and behavior. In juvenile females, endogenous estrogens are essential for growth and maturation of the female reproductive tract (Alonso and Rosenfield, 2002). In postpubertal females, estrogens act to regulate estrous or menstrual cycling in coordination with progesterone (P_4) and gonadotropins from the anterior pituitary gland. Rises in E_2 during the follicular phase of the cycle, among other actions, stimulate endometrial growth in the uterus (e.g. Garcia et al., 1988) and trigger a mid-cycle surge in luteinizing hormone (LH) from the anterior pituitary. LH in turn induces ovulation (e.g. Ferin et al., 1969; Meikle et al., 2001; Robker and Richards, 1998) and release of P_4 during the luteal phase of the cycle (Butcher et al., 1974; Freeman, 2006). In many mammals, actions of E_2 at the hypothalamus are critical for the induction of female sexual receptivity (e.g. Pfaff, 1980), which is enhanced by an acute LH-induced surge in P_4 (e.g. Barfield and Lisk, 1974; Beach, 1942). Following fertilization, E_2 influences the rate of passage of fertilized ova through the fallopian tubes (e.g. Ortiz et al., 1979) and has major influences over the receptivity of the uterus to blastocysts, determining the duration of the implantation window (Ma et al., 2003; Rajabi et al., 2014).

Inter-individual transfer of E_2 and other sex steroids

Natural steroid actions have always been assumed to occur within the individual whose glands produce these steroids. My laboratory has recently demonstrated that E_2 and other sex steroids can readily pass between cohabiting individuals, arriving in reproductive organs and areas of the brain where they can have potent actions on physiology and behavior.

First, consider pharmacological data showing that small lipophilic molecules, whatever their source, can readily enter circulation after dermal or nasal exposure. Transdermal absorption of small molecules into circulation is dependent on factors including molecular mass, solubility, and polarity (Schaefer et al., 1982; Wester and Maibach, 1983). This has been demonstrated for several steroids (Guzzo et al., 2012; Hueber et al., 1994; Scheuplein et al., 1969; Waddell and O'Leary, 2002). Nasal absorption of small molecules is facilitated by the large surface area, absorbent endothelium, and highly vascularized mucosa of the nasal membrane (Türker et al., 2004). While molecules under 300 Da with various physicochemical properties may enter circulation after nasal exposure, being lipophilic facilitates absorption of larger molecules (Arora et al., 2002). Lipophilic molecules may also be able to pass from the nasal cavity across the cribriform plate directly into the cerebrospinal fluid (Sakane et al., 1991), thereby directly reaching the brain. Given that they are highly lipophilic with low molecular mass, steroids such as E_2 (272.4 Da), testosterone (288.4 Da), and P_4 (314.5 Da) satisfy the conditions for transdermal and nasal absorption. Guzzo et al. (2012) found that when tritiated (^{3}H-) versions of these steroids with equivalent doses of radioactivity (in μCi) were applied to the nasal area of female mice (*Mus musculus*), ^{3}H-E_2 transferred much more readily than did ^{3}H-testosterone or ^{3}H-P_4. Bawarshi-Nassar et al. (1989) found that the majority of E_2 that was administered nasally to rats (*Rattus norvegicus*) was bioavailable as unconjugated E_2 in circulation, with the remainder likely being oxidized to the less active estrogen, E_1. Anand Kumar et al. (1974, 1982) demonstrated that nasal administration of E_2 or P_4 in the rhesus monkey (*Macaca mulatta*) produced higher levels in cerebrospinal fluid than did intravenous administration of the hormone, consistent with rapid and preferential passage to the brain.

Our laboratory recently provided the first demonstrations that E_2 can transfer directly between cohabiting conspecifics, being excreted by one and absorbed by another. We gave intraperitoneal injections of ^{3}H-E_2 to male mice in quantities that were miniscule relative to their endogenous levels of E_2, then traced radioactivity into the circulation, reproductive organs, and brain of cohabiting female mice (Guzzo et al., 2010, 2012, 2013). In males directly injected with ^{3}H-E_2, radioactivity was much greater in bladder urine than in any other fluid or tissue, and remained evident in urine samples for at least 24 h after the injection. After 3 days of cohabitation with such males, significant radioactivity was found in untreated females' blood, uterus, ovaries, muscles, olfactory bulbs, mesencephalon and diencephalon, and