Review

Sex Hormones' Regulation of Rodent Physical Activity: A Review

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There is a large body of emerging literature suggesting that physical activity is regulated to a varying extent by biological factors. Available animal data strongly suggests that there is a differential regulation of physical activity by sex and that the majority of this differential regulation is mediated by estrogen/testosterone pathways with females in many animal species having higher daily activity levels than males. The purpose of this manuscript is to review the mechanisms by which estrogen, progesterone, and testosterone affect the regulation of physical daily activity. This review lays the foundation for future investigations in humans as well as discussions about relative disease risk mediated by differential biological regulation of physical activity by sex.

Key words: estrogen, testosterone, progesterone, mammals, mice, physiology

I. Introduction

The use of animal models as proctors for human physiology has a long and significant history. Subsequently, some researchers have turned to using animal models to increase understanding of the mechanistic underpinnings of exercise behaviors. This work is critical given the literature that indicates a general decline in physical activity [50] and an increase in obesity and other hypokinetic diseases in most Western-cultures [27]. While physical activity has normally been considered a 'voluntary activity', held to free-will and influenced solely by environmental factors there is a growing body of literature that suggests that physical activity is significantly regulated by biological factors. These biological regulating factors may take many forms including a central nervous center-located "activity-stat" [38], an increase or decrease in various physiological substance or structures (e.g. GLUT4 ref. [51]), and/or genetics [23, 25, 46]. Biologically, the sex hormones play a large role in regulating various physiological parameters in both males and females and thus would be the natural subject of investigations into possible roles they play in regulating physical activity. Therefore, the focus of this paper is to review the literature investigating the effect of and the physiological mechanisms through which estrogen, progesterone, and testosterone may regulate physical activity. Given the sparseness of the human literature in this area, the primary model used in this research has been animal models.

II. Sex differences in physical activity

In general, it is commonly accepted that human females are less active than males; this sex differentiation in activity is prevalent in both children and adolescents [31] as well as adults [50]. However, confounding factors in human research in this area, including the well-known difficulty of accurately measuring physical activity in large populations [42], the complexity of giving hormone treatments in a physiologically-relevant and ethical manner [52], the general lack of well-controlled prospective human studies in this area, and the near impossibility of controlling environmental variations that can influence activity levels make understanding human sex differences in activity extremely problematic. Given these difficulties and the relative ease of experimental control in animal studies, it is appropriate to consider whether there is a sex difference in activity present in animal models.

The rodent literature that addresses sex hormone effects on activity generally shows that female rodents are more active than male rodents. Figure 1 is a summary of representative literature that has observed sex differences in daily activity in rats or mice. Overall, female rodent activity levels on a daily basis range from 20% to over 50% higher than males. Bronstein, et al. [6] observed that female Sprague-Dawley rats traversed significantly more distance during open-field testing (ranging from 28-46% more) than male rats, regardless of whether the animals had been handled or not. Craft, et al. [8] while considering sex differences in morphine-induced locomotor changes, observed that in the baseline state, female Sprague-Dawley rats exhibited 46% - 72% more activity (as measured by photobeam breaks in their home cage) than males over a 3-5 hour period, depending upon

whether they had been handled or not. Li, et al. [24] showed that there may be strain differences in these sex-related patterns of activity by showing that while the total path length that Wistar and WKY rats ran were significantly higher in females, there were no observed differences between sexes in the SHR rats. An earlier strain screen study in mice [25] showed that while overall female mice ran approximately 20% further per day than male mice, there was large variability in this percentage depending upon which of the 13 strains were tested. The percentage difference between female and male mice of the same strain in distance run on a daily basis ranged from -21.9% (SPRET/EiJ) to 111.2% (C3H/HeJ). Similar variation was also observed in duration and speed phenotypes. This type of between strain variation in photobeam break activity data has also been observed by Seburn within the Mouse Phenome database [41]. Earlier work by Koteja, et al. [21] monitored wheel running activity in both control Hsd:ICR mice and mice from generation 10 of an ongoing study to selectively breed mice for wheel-running activity. While there were significant differences between the control and selected lines in daily wheel-running activity, there were also significant sex-differences in the amount of distance run reported in both the control lines (50% higher in females) and the selected lines (58% higher in females). Recent work from our laboratory [26] with a large cohort of F_2 animals (n=310) developed from reciprocally breeding high active C57L/J and low active C3H/HeJ inbred mouse strains have shown that on average (over 21 days), the female animals ran 47% farther, 39% longer, and 9% faster than male animals.
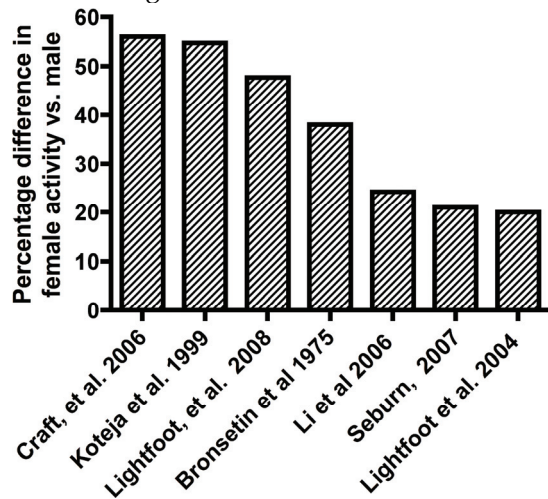

Figure 1 – Representative literature reporting percentage difference in female activity vs. male activity in rodents.

In summary, the majority of the animal literature over the past 80 years, have largely accepted that physical activity can be governed by biological factors and thus, activity levels are routinely treated as the dependent variable in many study designs. Additionally, given that most environmental factors can be controlled when using animal models, the animal literature has appropriately focused upon the role that sex hormones play in regulating daily activity, as Gorzek, et al. [15] did in investigating the effect of estrogen on daily activity levels.

III. Effects of sex hormones on activity in animal models

The investigation of the effect of sex hormones on physical activity in rodent models has a long and varied history. Figure 2 (R. Bowen personal communication) shows the interesting waxing and waning of such research over the past 80 years. While a complete historical review of this topic is outside the scope of this paper, it is of note that the consideration of sex hormone effects on activity was initiated in the early 1920's when it was found that ovariectomies significantly decreased activity in female rats in conjunction with the observation of a marked decrease in wheel-running activity in male rats after castration [18, 35, 44]. These studies also noted that implantation of ovarian tissue into both female rats [35, 44] and male rats [54] 'recovered' the pre-neutering activity patterns whereas implantation of testes into both male and female rats increased activity to a lesser extent than the ovarian implants [36]. The evidence from these studies, produced before estrogen, progesterone, or testosterone were isolated and identified, were so strong that one researcher concluded that in female rats, "Obviously, therefore, the spontaneous activity is dependent on ovarian function". However, this same researcher cautioned that none of the available experiments proved that the "hormone actually *produces* activity" (their emphasis) [35].
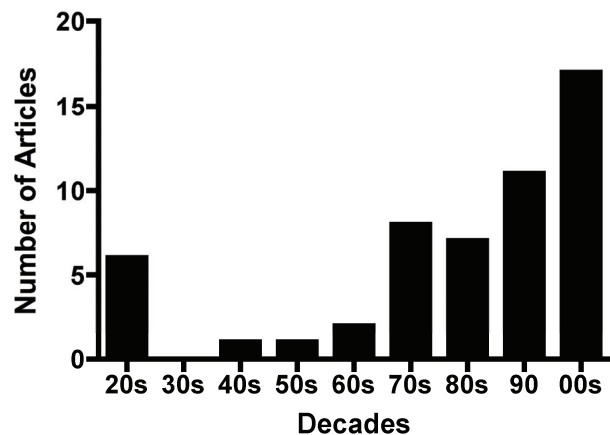

Figure 2 – The yearly distribution of studies regarding the effect of sex hormones on physical activity. The x-axis designates the ten-year period in which the studies were published. (Personal communication from R. Bowen)

Several studies since these early findings have shown that estrogen and testosterone directly impact spontaneous activity in rodent models. For example, recently Gorzek and colleagues [15] showed that while ovariectomies reduced daily wheel-running activity in female mice, a dosage of 3 $\mu g \cdot d^{-1}$ of 17β-estradiol increased activity to a level comparable to activity in sham-operated mice. Roy and Wade [39] demonstrated that administration of varying doses of testosterone propionate (100μg-1mg/day) increased running wheel activity in castrated male rats. These two studies, which are two examples of numerous studies, provide evidence of a cause/effect relationship between reproductive hormones and spontaneous activity in rats and mice.

Estrogen

While several studies have observed a causal relationship between the sex hormones, particularly estrogen, and spontaneous activity, the mechanistic underpinnings of this relationship has been somewhat unclear. Cushing, in a series of experiments (summarized by ref. [9]), investigated the role of sexual receptivity on the relationship between estrogen and activity using prairie voles. Female prairie voles, unlike other female rodents, are unique in that they undergo induced estrus by exposure to male voles and their sexual receptivity does not require progesterone, thus, removing two possible confounding factors that might influence activity. Cushing and Hite [9] found that sexually mature virgin female voles did not increase seven-day wheel running behavior either with or without estradiol injections (0.05μg or 0.5μg estradiol). It had been earlier shown that the number of estradiol receptors in the brain had previously been shown to increase in female voles when exposed to males [7]. Thus, the observation of a the lack of an increase in spontaneous activity with estradiol administration before exposure to males suggested that estradiol's effect on spontaneous activity was linked to the increased number of estradiol receptors in the brain.

Most research investigating the mechanisms of estrogenic increases in activity have focused on central neural pathways [12, 13, 30]. Bilateral implantation of estradiol in the medial preoptic area and the anterior hypothalamus was shown to variably increase wheel running activity in ovariectomized female rats [12]. Since the preoptic area contains both estrogen receptor isoforms - alpha (ERα) and beta (ERβ) – while the hypothalamic areas contain primarily ERα and little if any ERβ [43], Fahrbach, et al. [12] suggested that ERα may control the estrogenergic effect on activity. This hypothesis was difficult to test since 17β-estradiol has a similar affinity for both ERα and ERβ receptor

subtypes [22].

Coumesterol is a phytoestrogen with similar affinity as 17β-estradiol for ERβ, but four-fold less affinity for ERα and seven-fold higher affinity for ERβ than for ERα [22]. Garey and colleagues [13] injected coumestrol (10 μg), singly and in combination with estradiol implants (2.5μg) in 48 adult, ovariectomized Swiss-Webster mice and measured running wheel activity for the following 10 days. Running wheel activity increased with estradiol administration (Fig. 3), but coumestrol administration did not alter running wheel behavior as compared to a placebo injection. From this data, the authors suggested that the ERβ-pathway did not influence spontaneous activity; rather, the increases in spontaneous activity arising from estrogen administration were mediated primarily through the ERα pathway. Additionally, Garey, et al.'s data also eased concerns that the phytoestrogens in the standard rodent chows that have been used in many of the published rodent activity papers (e.g. [20, 21, 23, 25, 47, 48, 53]) have not confounded the conclusions of these studies as has been noted for other areas of rodent physiology (e.g. [45]).
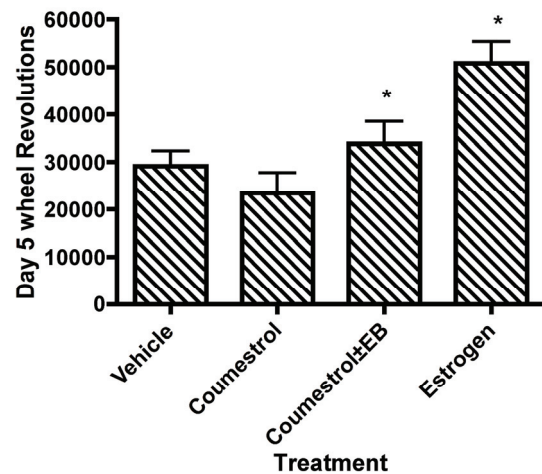

Figure 3 – Wheel running behavior after five days of phytoestrogen supplementation. *Significantly different from vehicle/placebo treatment. Drawn from tabular data presented by Garey, et al. [13].

Garey and colleagues' [13] suggestion that the estrogen-induced increases in spontaneous activity are mediated through the ERα pathway has been supported by further experiments with knock-out animals. Ogawa, et al. [30], using gonadectomized knock-out mice that lacked either ERα or ERβ genes, implanted either a 17β-estradiol capsule (16 or 160 ng/d) or a placebo capsule and monitored running wheel activity for nine days. Ogawa and colleagues observed that both male and female wild-type mice (i.e. with ERα and ERβ pathways intact) increased

running wheel activity significantly with either 16 or 160 ng/d estradiol treatments as compared to placebo mice. Additionally, with estradiol treatments, both sexes of the ERβ knock-out mice also significantly increased their running wheel activity compared to placebo; however, even with estradiol administration, the ERα knock-out mice did not increase activity compared to placebo. These results, in conjunction with Garey, et al.'s earlier study on coumesterol [13] lend strong evidence to the hypothesis that the estrogenic effects on running wheel behavior in mice are mediated through the ERα-pathway.

While it appears that estrogenic activation of the ERα-pathway is the primary mediator of the increase in running wheel behavior, the mechanisms through which the ERα-pathway influences activity are unclear. Morgan, et al. [28] have speculated that the ERα-pathway modulates several neurotransmitters, including dopamine and/or serotonin, which may play a role in the regulation of activity. In a review of the interactions of the sex differences in dopaminergic regulation, Becker [3] proposed that in female rats, estrogen enhanced terminal release of dopamine relative to male rats, which explains, the authors note, many reproductive-related behaviors such as increased pacing behavior. Additionally, it has been observed that estrogen can regulate several different steps in dopaminergic functioning, including dopamine release and metabolism as well as the pre- and post-synaptic receptor and transporter functioning (for review see [10]). Interestingly, effects of estrogen on dopamine receptors and transporter mechanisms in the nucleus accumbens have been noted to be as fast as two minutes; faster than would be expected from genomic activation [49] suggesting an influence of estrogen on the dopaminergic systems not arising through activation of either the ERα or ERβ pathways. Supporting this nongenomic activation hypothesis are observations of nongenomic effects of estrogens postulated to occur through the activation of a common membrane binding site with the same pharmacological profile as the hypothesized γ-adrenergic receptor [29].

Whether a differential activation of the dopaminergic systems by the ERα pathway or some other nongenomic pathway leads to the sex-related difference in activity levels is currently unknown. However, the involvement of dopamine in regulating daily activity is supported by indirect evidence. Garland's group [33, 34] have suggested that an alteration in dopaminergic functioning is one of the primary characteristics of mice experimentally evolved for high activity. Specifically, Rhodes and Garland have observed that an inhibition of dopamine transporter (DAT) will reduce the wheel-running of mice that are high active [34]. Additionally, they have shown that female high active mice have a reduced functioning of the D1 and D5 dopamine receptors [33]. Whereas Rhodes and Garland only studied female mice in each of their studies, it is yet to be determined if these alterations in dopaminergic functioning are different in male high active mice. Thus, while tenuous evidence suggests that the estrogen activation of the ERα-pathway and a possible nongenomic pathway may lead to an enhanced release of dopamine in female rodents which coupled with alterations in dopamine transport and/or receptors, may lead to increased activity, it is unclear whether this results in differential levels of activity between sexes.

Progesterone

While there have been numerous investigations of estrogen's role in determining physical activity levels in animal models, there have been virtually no studies considering whether progesterone influences activity. Progesterone is known to impact several physiological mechanisms and given that estrogen and progesterone normally cycle together during at least one portion of the female reproductive cycle [16], progesterone could also affect activity behavior. In a larger study concentrating on the differential effect of estradiol and estrone on activity, Young and Fish [55] noted that progesterone injected in conjunction with estradiol did not influence activity in rats in any manner. This result was expanded upon in a three-phase study conducted by Rodier [37] which is the only other currently available study in this area. Sherman albino rats received varying dosages of progesterone (4, 8, or 40 mg/kg/day) or placebo injections. Rodier noted that injections of 8 or 40 mg/kg/day in gonadally-intact rats decreased normal wheel-running activity, but neither an injection of 4 mg/kg/day progesterone or placebo solvents changed normal activity levels. Rodier then ovariectomized seven of the rats, injected them with 40 mg/kg/day progesterone for six days and then injected them with solvent for another six days. After ovariectomy, activity decreased to a level similar to that seen with progesterone injection in intact animals and was not further depressed with subsequent progesterone injection suggesting that progesterone was interfering with endogenous estrogens' effects on physical activity. To determine if exogenous estrogen interacted with the progesterone inhibition of wheel-running activity, Rodier then injected 17β-estradiol (100 μg/kg) into the ovarectomized and control animals, with each injection separated by five days. Eight days after the last estradiol injection, he injected either progesterone (40 mg/kg/day) or a pla-

cebo. While the estrogen injections increased the animals' running wheel behavior for at least 21 days after the first injection, the animals receiving the progesterone injections sharply decreased their activity, which then increased again after the cessation of the progesterone injections. Thus, given that either intrinsic or extrinsic estrogen had to be present for the inhibitory effects of progesterone to be observed, Rodier suggested that the progesterone decrease in physical activity was mediated through a direct interference with estrogen. A negative interference of progesterone on estrogenergic effects on neurotransmitters has been observed in both rats [17] and primates [14]; conversely, there is also literature available suggesting that progesterone augments [4] or has no effect [2] on estrogenic effects on neurotransmitters. However, an interference of progesterone on estrogen's physical activity effects is attractive to hypothesize because such an interference would explain the common sinusoidal activity pattern observed in female rats [35]; it could be suggested that peak activity was occurring during the follicular phase due to the primacy of the estrogen peak with the subsequent decrease in physical activity occurring during the luteal phase when progesterone is the dominant hormone and is interfering with estrogen's activity increasing effects. The dearth of investigations in this area leaves this and other hypotheses related to progesterone and estrogen's interactions on activity, such as the role of physiological doses of progesterone in activity regulation and the specific site(s) and mechanism(s) of the estrogen/progesterone interference open for further investigation.

Testosterone

In rodents, several studies using orchidectomized males have indicated a potential role for sex hormones in the regulation of activity [5, 36, 39]. For example, Broida and Svare [5] showed that locomotor activity – measured by photobeam breaks - could be rescued in castrated animals by implanting silastic capsules containing testosterone. Additionally, Broida and Svare suggested that there may be a genotype dependency in these responses, since they observed a larger decrement in physical activity after castration in inbred C57BL/6J mice as compared to inbred DBA/2J and random-bred Rockland-Swiss mice [5].

While a possible role for testosterone in the regulation of daily activity has been proposed [5, 36, 39], few studies have attempted to determine mechanistic causes of this effect. Roy and Wade [39] in a widely quoted study, injected either testosterone (100 µg/day), estradiol (10 µg/day), dihydrotestosterone propionate (DHTP - 100 µg/day), or sesame oil (placebo) into 20 castrated adult male Sprague-Dawley

rats and then monitored running wheel activity for 16 days. They noted that testosterone injections significantly increased the running wheel activity of the rats ($p<0.05$) but not as much as estradiol injections ($p<0.02$). Neither the DHTP or placebo injections increased running activity above baseline. Given that testosterone is aromatizable to estrogen whereas DHTP is not, the authors concluded that the primary mechanism regulating running wheel activity with testosterone administration was the aromatization of the testosterone into estrogen. In the second part of this experiment [39], these authors found that administration of an estrogen antagonist (MER-25) attenuated the increased running wheel activity resulting from either estradiol or testosterone injection. These results further supported the hypothesis that the increased activity from testosterone injection was mediated by the estrogen pathways.

While it appears that testosterone injections/implants can rescue activity levels after orchidectomy, supplementation of testosterone in intact animals does not increase physical activity levels. Eleftheriou and colleagues observed that testosterone level was not significantly correlated to a single 24 hour observation of wheel-running activity [11] in gonadally intact male C57BL/6By and Balb/cBy mice, in seven recombinant inbred strains (CXBD, CXBE, CXBG, CXBH, CXBI, CXBJ, and CXBK) or in two F_1 hybrid strains (B6CF$_1$ and CB6F$_1$). Salvador, et al. [40] showed that suprapharmacological doses (3.75, 7.5, 15, or 30 mg/kg) of artificial anabolic-androgenic steroids (testosterone propionate and nandrolone decanoate), injected into gonadally intact male OF1 male mice, did not affect running wheel activity measured 24 hours after the injection. Furthermore, mice injected with suprapharmacological doses for 10 weeks, did not show alterations in activity levels compared to baseline during 24 hour monitoring periods in the eight, ninth, or tenth week. These results support work in rats by Li and Huang [24] that showed that testosterone injections in both male and female gonadally-intact animals did not generally result in an increase in total path length. Thus, while work in gonadally-deficient animals has shown that testosterone, after aromatization to estrogen, will increase physical activity levels in rodents, supplementation above baseline levels will not further increase activity.

V. Summary

A wide-variety of evidence suggests that in rodents, females are generally more active than males, with a large proportion of this differential activity explained by sex hormone effects. The mechanism of this regulation (Fig. 4) appears to be mediated through the

estrogen-α receptor pathway with the requirement of aromatization of testosterone to estrogen in males. Little literature exists to explain the mechanism leading from estrogen-α receptor activation to an increase in activity; however, recent literature has suggested that alterations in dopaminergic systems as well as possible non-genomic actions of estrogen may be involved. The few available human studies in this area [1, 19, 32] have contained multiple confounders that make deriving any useful conclusions from these studies difficult at best. Thus, extensions of the existing mechanistic studies on ERα-pathway regulation of physical activity in rodents as well as more carefully controlled human studies are needed to determine if sex hormones provide any physiological regulation of activity in humans and if so, possible pathways through which this effect may be mediated. The increasing rate of inactivity which has led to the increased cardiovascular and other hypokinetic diseases in most populations [27] make understanding the mechanisms of physical activity regulation critical in the context of the health-related goals of our society.
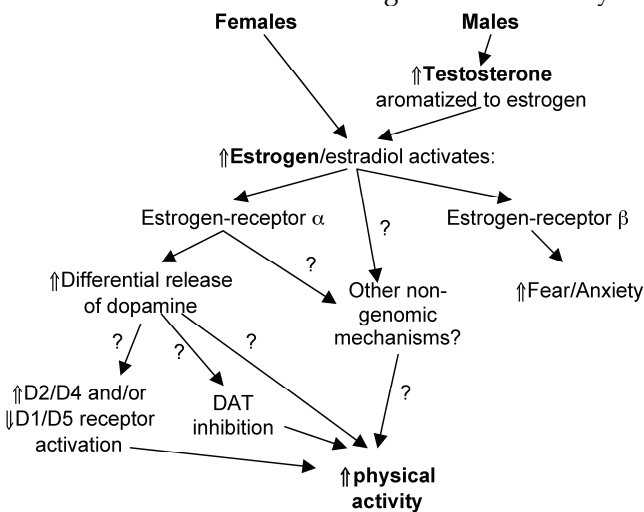

Figure 4 – Hypothesized schematic of the regulation of physical activity by sex hormones in rodents. "?" = pathway currently supported by speculation and/or tentative data. DAT = dopamine transporter; D2/D4, D1/D5 signify different dopamine receptor populations.

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Conflict of interest

The author has declared that no conflict of interest exists.

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