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Review article

Estrogen involvement in social behavior in rodents: Rapid and long-term actions

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ABSTRACT

This article is part of a Special Issue ("Estradiol and cognition").

Estrogens have repeatedly been shown to influence a wide array of social behaviors, which in rodents are predominantly olfactory-mediated. Estrogens are involved in social behavior at multiple levels of processing, from the detection and integration of socially relevant olfactory information to more complex social behaviors, including social preferences, aggression and dominance, and learning and memory for social stimuli (e.g. social recognition and social learning). Three estrogen receptors (ERs), ERα, ERβ, and the G protein-coupled ER 1 (GPER1), differently affect these behaviors. Social recognition, territorial aggression, and sexual preferences and mate choice, all requiring the integration of socially related olfactory information, seem to primarily involve ERα, with ERβ playing a lesser, modulatory role. In contrast, social learning consistently responds differently to estrogen manipulations than other social behaviors. This suggests differential ER involvement in brain regions important for specific social behaviors, such as the ventromedial and medial preoptic nuclei of the hypothalamus in social preferences and aggression, the medial amygdala and hippocampus in social recognition, and the prefrontal cortex and hippocampus in social learning. While the long-term effects of ERα and ERβ on social behavior have been extensively investigated, our knowledge of the rapid, non-genomic, effects of estrogens is more limited and suggests that they may mediate some social behaviors (e.g. social learning) differently from long-term effects. Further research is required to compare ER involvement in regulating social behavior in male and female animals, and to further elucidate the roles of the more recently described G protein-coupled ERs, both the GPER1 and the Gq-mER.

Contents

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Introduction

Estrogens influence an array of social behaviors essential for appropriate behavioral functioning and for the success of gregarious animals. The neurobiology of social behaviors and in particular how they are influenced by gonadal hormones has been investigated mostly in rodents. This review will consider estrogens' effects on four commonly studied behavioral categories that assess different aspects of social behavior: social recognition, social learning, social preference and responses, and agonistic behaviors. A number of these studies have incorporated an ethological approach that takes advantage of the natural behaviors of the animals, thus allowing for a comprehensive analysis of factors that can influence behavior, and providing valuable information about the regulation of social systems that may be translatable to humans (Blanchard and Blanchard, 1988).

Living in a social group imposes various cognitive demands on animals. This includes factors such as social recognition and social learning, both of which have been shown to be enhanced by estrogens. Social recognition can be defined simply as an animal's ability to distinguish between novel and familiar individuals (Choleris et al., 2003, 2006; Imwalle et al., 2002; Phan et al., 2011, 2012a; Sánchez-Andrade and Kendrick, 2011; reviewed in Choleris et al., 2008, 2012). It can also be extended to include the recognition of individuals based on factors such as kinship, reproductive state, health and infection status, or ranking in a social hierarchy (reviewed in Choleris et al., 2009; Gabor et al., 2012). Social recognition learning, or acquiring information about conspecifics, is thus a form of social information processing that is essential for an animal's successful participation in its social group.

As social recognition consists of an animal investigating a conspecific to acquire information *about* that conspecific, it is considered to be a type of individual learning. In contrast, social learning can by-pass individual experiences by allowing one to acquire information *from* a conspecific through observation or direct social interaction (Galef, 1989). This broad categorization of social learning encompasses many behavioral responses that are driven by socially-acquired information, including mate choice copying (Brown and Laland, 2003; Galef, 1989; Galef and White, 2000; Galef et al., 2008; Kavaliers et al., 2005; White, 2004), predator and parasite avoidance (Brown and Laland, 2003; Griffin, 2004; Kavaliers et al., 2003, 2005; Whiten and Mesoudi, 2008), and foraging behavior (Brown and Laland, 2003; Galef, 1989; Valsecchi and Galef, 1989). Social learning allows animals to circumvent the potential risks of individual, trial-and-error learning, and can thus serve as an adaptive learning strategy (Choleris et al., 2012; Galef, 1989). As such, social learning can be considered an advantage of social living, while social recognition learning is a necessity.

Along with their effects on the learning and memory of social factors, estrogens also affect how an animal interacts with others. Estrogens can affect the most basic form of sociality, social approach or avoidance, and an animal's motivation to interact with a conspecific (reviewed in Choleris et al., 2009, 2012). Estrogens can also modulate more complex social interactions such as social, mate, and sexual choices and agonistic behaviors (Kavaliers et al., 2004a, 2004b, 2004c; reviewed in Choleris et al., 2012). Both male and female rodents display agonistic behaviors, including behaviors that are related to dominance and aggression (Clipperton-Allen et al., 2010, 2011; Scordalakes and Rissman, 2003). Agonistic behaviors allow an animal to obtain and maintain a territory, establish itself in a social hierarchy, and gain competitive advantages, such as access to reproductive opportunities and foraging sites (Adams and Boice, 1983; Blanchard et al., 2001). All of these social behaviors require the use of multiple cues, with olfactory information being especially important in rodents.

Estrogens' effects on behavior are mediated by their action at estrogen receptors (ERs). The most commonly studied ERs include the classical receptors ERα (a.k.a. ESR1, NR3A1) and ERβ (a.k.a. ESR2, NR3A2), which are similar in their structure but encoded by genes on different chromosomes (Heldring et al., 2007), with both overlapping distribution in the brain and differences in location and levels of expression (Micevych and Dominguez, 2009). More recently, G protein-coupled ERs have been described, including the GPER1 (a.k.a. GPER, GPR30) (Brailoiu et al., 2007) and the STX-responsive Gq-mER (Christensen and Micevych, 2013; Kenealy et al., 2011; Nag and Mokha, 2014; Roepke et al., 2011; Smith et al., 2013), though the effects of the GPER1 on behavior have been more thoroughly investigated thus far (Hammond et al., 2009, 2012; reviewed in Ervin et al., 2013). Through action at these receptors, estrogens can have both long-term effects on behavior, involving gene transcription and occurring hours to days after hormone manipulation (reviewed in Choleris et al., 2008; Frick, 2012), and rapid effects, which instead involve intracellular signaling cascades occurring from as early as 15 min, up to about 2 h, after hormone manipulation (Filardo and Thomas, 2012; reviewed in Frick, 2012; Luine and Frankfurt, 2012; Luine, 2014; Nilsson et al., 2001; Sellers et al., 2014; Vasudevan and Pfaff, 2008). This review will provide an overview of estrogens' involvement in social cognition and behavior focusing on rodents: (i) administered exogenous estrogens or ER agonists, (ii) lacking the genes for the ERs or aromatase, the enzyme responsible for estradiol synthesis from its precursor testosterone, (iii) selective regional silencing or activation of ERs, and (iv) in female animals during their estrous cycle or other reproductive phases when circulating estrogens are naturally high or low.

Estrogens, odors, and social responses

Chemical communication and olfactory signals play an important role in the regulation of social behaviors in mammals. Odors both provide information about others and convey information to others. Chemical communication in mammals is very flexible and dependent on the social context. Behavioral responses to other individuals are driven by social cues, especially odors, often acquired and associated with initial appraisal rather than through direct interactions with that individual (Kavaliers et al., 2014). Social information alone, independent of social interactions, can influence behavior and the activity of various brain areas (e.g. Desjardins et al., 2010). In rodents, odors provide conspecifics