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Review

Estrogenic involvement in social learning, social recognition and pathogen avoidance

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ABSTRACT

Sociality comes with specific cognitive skills that allow the proper processing of information about others (social recognition), as well as of information originating from others (social learning). Because sociality and social interactions can also facilitate the spread of infection among individuals the ability to recognize and avoid pathogen threat is also essential. We review here various studies primarily from the rodent literature supporting estrogenic involvement in the regulation of social recognition, social learning (socially acquired food preferences and mate choice copying) and the recognition and avoidance of infected and potentially infected individuals. We consider both genomic and rapid estrogenic effects involving estrogen receptors α and β, and G-protein coupled estrogen receptor 1, along with their interactions with neuropeptide systems in the processing of social stimuli and the regulation and expression of these various socially relevant behaviors.

1. Introduction

Depending upon the ecology of a certain species social aggregation may or may not be evolutionarily favored, with the costs and benefits varying under different conditions (extensively reviewed in [26,269,306]). Examples of the benefits of social grouping are a reduction in the risk of predation, increased feeding efficiency, better localization of important resources such as breeding sites, thermoregulation, sharing of parental cares and territory defense, and several others. Examples of the costs of social aggregations are the increased competition for key resources such as food, mates and breeding sites, and the enhanced risk of the spread of diseases and parasites. These costs can either prevent the evolution of group living or, in social species, they can greatly affect behavior including social interactions and mating preferences, and thus become a major evolutionary pressure on the individuals belonging to social species. For example, in 1976 Freeland [95] proposed that social organization and social processes were heavily influenced by parasites. He suggested that aspects of primate social behaviors and interactions have evolved to reduce the spread of new and existing parasites and disease. As such, social behavior has been shaped by pathogen pressure, with animals, including humans, having evolved a variety of mechanisms and adaptive behavioral responses to recognize and minimize their exposure to individuals that can pose a threat of contagion. This can include: recognition and avoidance of unfamiliar individuals and strangers, social distancing and territorial behavior to exclude conspecifics that may carry novel pathogens, modifications in sexual behavior to avoid mating with infected individuals, and specific behaviors to protect offspring from infection (examples in [148,211]).

When social aggregation is favored, different types and degrees of it can evolve, from highly solitary species to species that live in large colonies. Among the social species different levels and types of social organizations exist, from the loose aggregate of most herd species of savannah herbivores to the highly structured social organization of eusocial insects or most primate species. Living with others involves both general and specialized cognitive skills. For example, complex signals for effective intraspecific communication tend to evolve in social species, and social recognition and social learning processes can become very sophisticated [26]. Thanks to social recognition, most social species effectively use information about others and adaptively adjust their social behavior on the basis of such information. In addition, the presence of others can provide a source of adaptive information that can be acquired through social learning processes. While social recognition and social learning have been shown in a number of animal species (reviewed in [46,89,107]), in the laboratory they are most

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commonly investigated in two species of rodents, rats (*Rattus norvegicus*) and mice (*Mus musculus*/*Mus domesticus*), both of which are gregarious in the wild [22,81,178].

The neurobiological underpinnings of social cognition have been receiving increasing investigation and a number of neurotransmitter and neuropeptide systems have been implicated (see [42,271] for recent reviews). A key role for the sex hormones is also emerging. In particular, the steroid hormones, estrogens, appear to play a major role. Here, we first briefly introduce the estrogenic system, then we introduce and define social learning and social recognition and how these processes are involved in social animals' coping with the increased risk of parasitic exposure associated with sociality. Each of these will be followed by a review of studies that have investigated the roles of estrogens and their receptors in the regulation and expression of these behaviors.

2. Estrogens and their receptors

Estrogens are a class of steroid hormones synthesized in the gonads and in other organs from cholesterol via a series of chemical reactions that are part of the steroidogenic pathways. Estrogens affect both reproduction and non-reproduction related functions and behaviors. Behavioral effects are by and large mediated by actions in the brain (reviewed in [40,124]) both by circulating estrogens of gonadal origin and by locally synthesized hormones [62,135]. Estrogenic actions are mediated by a number of different receptors. The first discovered estrogen receptor (ER), today known as ERα, has been long known [141], while the second of the better-known ERs, ERβ, was discovered in the mid 1990s [171]. Subsequently, splice variants of ERα and ERβ have been described, which differ in their affinities for estradiol and distribution in the brain [124,282]. More recently, membrane-bound ERs (mER) have been described. The G-protein coupled estrogen receptor 1 (GPER1), previously known as G-protein coupled receptor 30 (GPR30), has been well characterized [36,92,188,204,238]. In addition, in recent years another estradiol-responsive, G-coupled membrane receptor has been described (Gq-mER) [241]. Even though its distribution is currently unknown, Gq-mER appears to be involved in maintaining homeostatic functions by reducing food intake and fat accumulation and increasing bone density [242,248,251]. Finally, in 2002 the existence of an additional mER, named ER-X, was hypothesized [288]. However, its gene sequence and amino acid structure are currently unknown.

Estrogens can have both long-term, genomic actions as well as rapid actions that are generally believed to be non-genomic. Genomically, estrogens act on cell functions via the activation of ERα and ERβ, which are part of the nuclear hormone receptors family. As such, upon binding with estrogens, ERα and ERβ dimers bind to the Estrogen Response Element (ERE) on the promoter of genes whose transcription they then regulate. Non-ERE-mediated effects were also shown and a number of co-activators also regulate estrogenic genomic actions. As well, the ERs have some ligand-independent transcriptional responses and can also interact with other transcription factors in regulating gene expression (recently reviewed in [282]). In addition to genomic effects, ERα and ERβ, as well as GPER1 and Gq-mER mediate rapid estrogenic actions that involve cell-signalling mechanisms, mostly the phosphorylation of various kinases and the regulation of intracellular calcium levels. For ERα and ERβ these rapid effects are mediated by cell membrane-bound or cytosolic versions of these receptors (recently reviewed in [250]). GPER1 instead is found in the cell membrane and other intracellular compartments, such as the endoplasmic reticulum or the Golgi complex [239,240,256] , [193,204] and is also involved in kinase phosphorylation [92,204] and intracellular calcium regulation [30]. Similarly, Gq-mER activates kinase phosphorylation [249,313] and affects calcium dynamics [168,172]. The cell signalling actions of estrogens' rapid effects can also ultimately affect gene transcription, usually by acting at nuclear factors other than the ERs [25]. Thus, an organism's responses to estrogens are generally the result of a complex interaction between genomic and non-genomic signalling (for further details see reviews [219,250,295]).

ERα, ERβ and GPER1 are all highly expressed in the brain, their distribution being both overlapping and unique (recently reviewed in [124]). Areas of overlapping ERα and ERβ presence are the medial amygdala (MeA), preoptic area, bed nucleus of the stria terminalis, nucleus of the solitary tract and periaqueductal gray. Areas of predominant ERα expression are the ventromedial nucleus of the hypothalamus and the arcuate nucleus. ERβ instead, predominates in the suprachiasmatic, supraoptic and paraventricular nuclei of the hypothalamus, the cerebellum, dorsal raphe, hippocampus and cerebral cortex [174,203,221,266–268]. GPER1 is highly expressed in the paraventricular and supraoptic hypothalamic nuclei, the anterior and posterior pituitary, striatum, hippocampus, substantia nigra, area postrema, nucleus of the solitary tract and dorsal motor nucleus of the vagus [30]. Expression of all ERs in areas of the "social brain" and areas involved in learning and memory processes can explain the described involvement of these receptors in both social recognition and social learning. The differential distribution further suggests that, like for other behaviors, the respective involvement of the three ERs in these two social cognitive processes may be different.

Pharmacological and genetic tools have been developed that permit the investigation of the specific role of the three estrogen receptors in social and other behaviors. Common pharmacological tool are the ERα agonist 4,4′,4″-(4-Propyl-[1*H*]-pyrazole-1,3,5-triyl) *tris*phenol (PPT), which has 410 times greater affinity for ERα than ERβ [276], and two ERβ agonists, 2,3-bis(4-Hydroxyphenyl)-propionitrile (DPN) and 7-Bromo-2-(4-hydroxyphenyl)-1,3-benzoxazol-5-ol (WAY200070). These two commonly used ERβ agonists show similar receptor specificity and neither is as selective for ERβ as PPT is for ERα. DPN is 70-fold more selective for ERβ than ERα [198], while WAY200070's affinity for ERβ in mice is 68 times that for ERα (compound 92 in [189]). In addition, GPER1-specific drugs have recently been developed. A GPER1 agonist (±)-1-[(3aR^*,4S^*,9bS^*)-4-(6-Bromo-1,3-benzodioxol-5-yl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl]-ethanone (G1) and a GPER1 antagonist (3aS^*,4R^*,9bR^*)-4-(6-Bromo-1,3-benzodioxol-5-yl)-3a,4,5,9b-3H-cyclopenta[c]quinoline (G15) appear highly specific for GPER1, with neither of them showing affinity for ERα or ERβ [28,73]. Finally, a Gq-mER selective ligand, STX [2-(4-hydroxyphenyl)-3-phenylpent-2-enoic acid[4-(2-dimethyl amino ethoxy)phenyl] amide, E-enantiomer], has been developed and used in studies on homeostasis [287]. Most behavioral investigations with these drugs have utilized systemic administrations (e.g. [53–55]; reviewed in [40]). Less commonly, direct brain infusions have attempted to identify their specific site of action (e.g. [38]).

Genetically modified mice in which one or a combination of the ERs has been rendered non-functional, gene knockout (KO) mice, have also been extensively used in neurobehavioral investigations. Mice with non-functional ERα (αERKO), ERβ (βERKO), both ERα and ERβ (αβERKO), GPER1 (GPERKO [191]), or aromatase (ArKO), the enzyme that converts testosterone to estradiol, have been developed and the αERKO, βERKO and ArKO mice were tested on various behaviors, including social behaviors ([48,137,218,234] reviewed in [40]). However, in these mice the gene is knocked-out throughout their lifetime and body (so-called 'global' KO mice), and their use faces issues intrinsic with the global KO technology (reviewed in [130]), that can lead to inconsistent results obtained with separately generated KO mice (e.g. βERKO mice, reviewed in