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Sex-specific development of spatial orientation is independent of peripubertal gonadal steroids

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Summary Prenatal exposure to androgens has been shown to modulate brain development, resulting in changed behavioral attitudes, sexual orientation and cognitive functions, including processing of spatial information. Whether later changes in gonadotropic hormones during puberty induce further organizational effects within the brain is still insufficiently understood. The purpose of this study was to assess development of spatial orientation before and after the time of normal pubertal development, in an ovine model where half of the animals did not undergo typical reproductive maturation due to the pharmacological blockade of gonadotropin releasing hormone receptor (GnRHR) signaling.

The study formed part of a larger trial and utilized 46 pairs of same sex Scottish Mule Texel Cross twins (22 female and 24 male). One twin remained untreated throughout (control) while the other received a subcutaneous GnRH agonist (GnRHa: Goserelin-Acetate) implant every fourth week. GnRHa treatment began at eight and 28 weeks of age, in males and females respectively, because the timing of the pubertal transition is sexually differentiated in sheep as it is in humans. Spatial orientation was assessed at three different time points: eight weeks of age, before puberty and treatment in both sexes; 28 weeks of age, after 20 weeks GnRHa treatment in males and before puberty and GnRHa treatment in females; and at 48 weeks of age, which is after the normal time of the pubertal transition in both sexes. Spatial orientation was tested in a spatial maze with traverse time as the main outcome measure.

GnRHa treatment did not affect spatial maze performance as no significant differences in traverse time between treated and untreated animals were observed at any time-point.

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Adolescent females (48 weeks of age) traversed the maze significantly faster than adolescent males, whereas no sex differences in traverse time were seen at earlier developmental stages (eight and 28 weeks). Development of sex differences in spatial orientation was independent of exposure to pubertal hormones since puberty-blocked and control animals both showed the same pattern of spatial maze performance. This result demonstrates the prenatal nature of spatial orientation development. Furthermore, the unexpected finding that female animals outperformed males in the spatial orientation task, underscores the importance of the testing context in spatial orientation experiments.

1. Introduction

Documentation of the long-lasting masculinization of mating behavior in female guinea pigs by prenatal testosterone exposure (Phoenix et al., 1959) led to formation of the hypothesis that hormones could have organizational effects on sex-specific behaviors (Williams and Meck, 1991). Numerous publications have since shown that such hormone exposure can lead to masculinization of activities, influence sexual orientation, personality traits and certain cognitive functions (Hines, 2011). Although these effects are mainly associated with prenatal androgen exposure, other developmental periods are receiving attention with regard to their organizational impact on brain development and behavior (Berenbaum and Beltz, 2011). In particular, the peripubertal period has been identified as a time when there are marked neuronal changes which may be correlated to sex hormone production and secretion patterns (Sisk and Zehr, 2005; Pfaff, 2009; Schulz et al., 2009). The timing and magnitude of these changes might be important in directing organizational activities within the brain (Schulz et al., 2009).

Today, exposure to pubertal hormones is frequently manipulated in pediatric medicine for therapeutical purposes in conditions such as central precocious puberty, idiopathic short stature, severe hypothyroidism, growth hormone deficiency, congenital adrenal hyperplasia, and even autism (Carel et al., 2009). Despite the demonstration of gonadotropin releasing hormone (GnRH) receptor expression throughout the brain (Skinner et al., 2009), and results of recent animal studies documenting physiological and cognitive effects of long term GnRH agonist (GnRHa) administration (Wojniusz et al., 2011; Evans et al., 2012), the potential side effects of such treatments on cognitive and behavioral development are virtually unknown (Carel et al., 2009). This is of significant clinical importance as many neuropsychiatric disorders, and behavioral and emotional problems are first observed during the peripubertal period (Eaton et al., 2008; Casey and Jones, 2010), but whether they or their development are influenced by pubertal hormones is unknown. Previously, using an ovine model, our group has demonstrated that pharmacological blockade of the pubertal transition with a GnRHa can influence the development of cognitive functions in a sex-specific manner, specifically affecting emotional regulation, risk-taking, and emotional reactivity (Wojniusz et al., 2011; Evans et al., 2012).

Spatial orientation has been frequently investigated in animal models. It represents an essential cognitive function as most mammals depend on it for finding food, mates, and avoiding becoming prey (Wolbers and Hegarty, 2010). Spatial orientation encompasses spatial ability, i.e. the capability to generate and recall spatial information (Voyer et al., 1995), but differs from spatial ability as it also involves the environment and therefore the ability of a subject to acquire information about its surroundings and navigate through them (Coluccia and Louse, 2004). The results of animal studies of spatial orientation typically indicate that it is sexually differentiated, with a male advantage (Jonasson, 2005) and that it is influenced by sex hormones (Wolbers and Hegarty, 2010). Human studies also statistically indicate a robust male advantage with regard to spatial ability (Linn and Petersen, 1985; Voyer et al., 1995; Platek et al., 2007; Hines, 2011) but less pronounced sex differences in spatial orientation (Coluccia and Louse, 2004). The results and the exact relationship between sex and spatial ability/orientation appear, therefore, to be significantly influenced by the task undertaken (for meta-analysis see Jonasson, 2005).

In the present study we wished to explore the effects of GnRHa on the development of this fundamental cognitive function. Firstly, we investigated the normal development of spatial orientation in an ovine cohort from an early age and through the pubertal transition, and compared it with that of their same-sex twins that had their puberty blocked by GnRHa. Secondly, by assessing spatial orientation at several time points, we aimed to explore when potential sex-differences became apparent and whether blockage of pubertal hormones interfered with the development of sex differences in spatial orientation.

2. Methods

2.1. Animals

All animal procedures were conducted at the University of Glasgow's Cochno Research Centre (55° 55′N) following review by the University's Welfare and Ethics Committee and in accordance with Home Office regulations (PPL 60/3826). All efforts were made to minimize animal suffering. To eliminate the possible developmental effects of steroid transfer between siblings of different sexes, the study was conducted using 46 pairs of same-sex twin lambs (Scottish Mule Texel Cross, 22 female and 24 male). Lambs were born between 17th March and 1st April 2008 and remained with their dams until weaned at about 12 weeks of age. Males and females were maintained separately during the entire study period. Within each set of twins, one was randomly assigned, at birth, to the control (C) and the other to the treatment (T) group. Although the onset of puberty and periodicity of fertility differ between sheep and humans, a similar interplay between neurosecretory cells of the brain and the peripheral sexual organs is well documented in vertebrates (mammals,