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Effects of inhibition of gonadotropin releasing hormone secretion on the response to novel objects in young male and female sheep

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Summary This study investigated the actions of blocking the GnRH receptor using a specific agonist on the response of male and female sheep to a novel object placed in their pen. The study is part of a series performed on 46 same sex twin animals. One of the pair received a subcutaneous implant of the GnRH agonist Goserelin acetate every four weeks while the other remained untreated. Implantation began immediately prior to puberty; at 8 weeks in the males and 28 weeks in the females (as timing of puberty is sex specific). To determine the effects of agonist treatment on the reproductive axis blood samples were collected for measurement of testosterone in the males and progesterone in the females. In addition the volume of the scrotum was determined. The present study aimed to determine whether there are sexually differentiated behavioural responses to a novel object at different stages of brain development (8, 28 and 48 weeks of age) and whether these responses are altered by GnRHa treatment. Approach behaviour towards and interactions with the novel object were monitored as was the number of vocalisations per unit time during the test period. GnRHa treatment suppressed testosterone concentrations and testicular growth in the males and progesterone release in the females. Sheep vocalised significantly more prior to weaning (8 weeks of age) than post weaning (28 and 48 weeks of age) suggesting stress on separation from their dams.

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Our current study shows that males are more likely to leave their conspecifics to approach a novel object than females. As this behaviour was not altered by suppression of the reproductive axis we suggest that, although sex differences are more obviously expressed in the phenotype after puberty, these may be developed during adolescence but not primarily altered during puberty by sex hormones.
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1. Introduction

Gonadotropin releasing hormone (GnRH) is a decapeptide synthesised in specialised neurons in the hypothalamus and released into the hypophysial portal vessels to act on receptors in the pituitary gland (Miller, 2005). It has been known for decades to play a key role in the control of reproductive function and behaviour. However, more recently, GnRH receptors have been found to be expressed in diverse non-reproductive tissues including the heart (Dong et al., 2011), bladder (Coit et al., 2008), skin (Reichler et al., 2008) and kidney (Kakar and Jennes, 1995) as well as in malignant cells (Harrison et al., 2004). Although the precise function played by these GnRH receptors is unknown, they may have important roles in normal physiology outwith their traditional roles in the regulation of reproduction.

Within the brain, GnRH receptors are also located in regions that are not primarily responsible for the control of the reproductive axis but involved in cognition such as, emotion regulation, memory and motor coordination, particularly areas of the cerebral cortex (Wilson et al., 2006) such as the hippocampus (Albertson et al., 2008a; Chu et al., 2010; Schang et al., 2011), amygdala (Jennes et al., 1988) and also in the cerebellum (Albertson et al., 2008b).

Currently, GnRH agonists (GnRHa) are used in a diverse range of clinical applications and long term treatments, are key medical interventions in prostate cancer, functional bowel disease, uterine leiomyoma and breast cancer. However, their use has been associated with cognitive side effects (Wilson et al., 2007; Nelson et al., 2008). In adult humans, as well as laboratory animal species, long term GnRHa treatment has been shown to lead to sex specifically changes in emotional and behavioural regulation (Wojniusz et al., 2011), processing of visuo-spatial information (Nelson et al., 2008; Wojniusz et al., 2013) and working memory (Grigorova et al., 2006; Palomba et al., 2008). Furthermore, under pathological conditions such as Alzheimer's disease cognitive function has been reported to be positively influenced by GnRHa treatment (Bowen et al., 2004; Casadesus et al., 2006). As a result of the increased clinical interest in GnRHa therapy's non-reproductive effects (Doraiswamy and Xiong, 2006) the focus of this paper is the impact of GnRH manipulation on cognition and behaviour.

While there is a growing body of research literature on the cognitive effects of long term GnRHa treatment in adults, there is a general dearth of information relative to its effects in children and adolescents, as highlighted in the published 'Consensus statement on the use of gonadotropin-releasing hormone analogues in children'' (Carel et al., 2009). This is despite the use of long term GnRHa treatment in children and adolescents for conditions such as central precocious puberty, idiopathic short stature, protection of the gonads in children undergoing cancer chemotherapy and in early onset gender identity disorder (Delemarre-van de Waal and Cohen-Kettenis, 2006).

Experimental evidence for the link between behaviour and gonadal steroids is sparse and difficult to obtain in our own species (Sherwin, 2009; Hines, 2010). Hence there is a need for good animal models. While rodents have been most widely used, the sheep is more like the human in the hormonal control of reproductive cycles and in having a relatively long developmental phase between birth and puberty. We have recently shown that long term prepubertal GnRHa treatment significantly impacted emotion and behaviour regulation in adolescent sheep and that the sexes were differently affected by GnRH modulation (Wojniusz et al., 2011; Evans et al., 2012).

The transition between human childhood and adulthood is a time when cognitive functioning alters rapidly, as developmental changes occur within the brain (Pharo et al., 2011). It is also a time when the risk of injury or death increases 2—3 times above that in childhood despite the good health of the subjects. It has been suggested that this is a result of developmental changes in impulsive behaviours such as risk-taking, perceptions of vulnerability and boldness/fear reactions, all of which have implications for decision making (Boyer, 2006). These behaviours may often become more pronounced in one sex around the time of adolescence and this is also true of animals (Cyrenne and Brown, 2011a,b). For example, impulsive and novelty seeking behaviours are more pronounced in male adolescents than females (Zuckerman, 2006), whereas fear/anxiety and avoidance behaviours are more common in females (Altemus, 2006). These observations suggest a link between the behaviours and the pubertal rise in gonadal steroid hormone release (Sisk and Zehr, 2005; Kuhn et al., 2010), particularly testosterone (Forbes and Dahl, 2010), concentrations of which are elevated in the adolescent and adult male compared with females of a similar developmental stage (Gupta et al., 1975).

In animals many behavioural tests have been devised to test risk-taking, novelty seeking, and approach/avoidance reactions and these include the novel object test (Berlyne, 1950). Variants of the novel object test are routinely used in rodents (Cyrenne and Brown, 2011a,b) but have also been used in farm animal species (Forkman et al., 2007). An animal's response to novel objects has been regarded as a test for fear, anxiety or peer-attachment (Romeyer and Bouissou, 1992; Forkman et al., 2007; Leiner and Fendt, 2011) as well as for novelty-seeking and risk-taking (Cyrenne and Brown, 2011a,b).

The present study aimed to determine whether there are sexually differentiated behavioural responses to a novel object at different stages of brain development (8, 28 and 48 weeks of age) and whether these responses are altered by GnRHa treatment. Three specific hypotheses were tested.

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