Control of breeding season by microvascular remodelling in the sheep.

The sheep is a seasonally breeding species in which reproductive activity is dependent on daylength. Information on day-length is translated to the body by the daily pattern of the hormone melatonin secreted by the pineal gland. Because light suppresses melatonin, this hormone is only produced at night, so encodes for day-length by providing an index of night-length. Melatonin exerts its effects on reproduction, in part, through its action on the pituitary gland, which contains glandular and neural components that regulate vital functions such as growth and metabolism, and reproduction. Chemicals produced in the hypothalamus control the release of hormones in the glandular part. These chemicals are transported from the hypothalamus to the pituitary in the blood, via a highly specialised blood vessel network known as the hypothalamic-pituitary-portal system. For the control of reproduction, gonadotrophin-releasing hormone (GnRH) is carried to the pituitary where it stimulates the release of two hormones, luteinising hormone (LH) and folliclestimulating hormone (FSH), from specialised gonadotroph cells. These hormones act on the testes in males and ovaries in females to promote the development of sperm and eggs, respectively, and the production of sex steroid hormones. The lactotroph cell is responsible for producing the hormone prolactin, which acts in the mammary gland to promote lactation, as well as in the gonads, the hypothalamus and the pituitary itself. Importantly, excessive prolactin is associated with infertility. Seasonal changes in day-length affect the secretion of LH and FSH, and prolactin. Interestingly, the annual patterns of LH/FSH and prolactin in sheep are opposite to each other. However, while melatonin acts in a region of the pituitary termed the pars tuberalis (PT), where most melatonin receptors are present, and it powerfully inhibits prolactin secretion, the lactotrophs, which produce prolactin, are only present in a different region of the pituitary, the pars distalis (PD). Moreover, although gonadotroph cells are contained in both the PT and PD, their function is dependent on GnRH stimulation from the hypothalamus. Thus, the melatonin signal conveying information on day-length must somehow be relayed to the pars distalis for the control of prolactin and to the hypothalamus for the control of GnRH/LH/FSH by transport within the pituitary by blood vessels, but how this is done is still not known. We recently discovered that the microcirculation of the sheep pituitary gland is highly dynamic, remodelling in response to day-length. This provides a possible mechanism for seasonal control of fertility. Vascular remodelling is governed by vascular endothelial growth factor (VEGF), a protein that controls the structure and permeability of blood vessels. Our previous work showed that two families of VEGF with opposing effects, i.e. stimulate or inhibit blood vessel growth, are normally produced, and that both families are present in the pituitary. This project will unravel whether melatonin controls production of these families of VEGF in the sheep pituitary, and the effects of their differential output on the seasonal secretion of prolactin and gonadotrophins. We will use a variety of techniques to determine how microvascular remodelling contributes to pituitary function - in this case to the control of seasonal breeding in sheep, but the same principles may also be relevant for the control of fertility in humans. Supervisor: Prof David Bates

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