セミナーのお知らせ

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場所　L2-307教室

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Novel Hypothalamic Neuropeptides Regulating the Reproductive Hormone Cascade

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The detection and integration of diverse exogenous environmental inputs (eg light, temperature, stress, visual, nutrients, toxins, odorants, pheromones and pathogens) and endogenous signals (eg hormones, growth factors, inflammatory and stress mediators, neurotransmitters, metabolites, ions, water and electrolytes and lipids) in the vertebrate brain is crucial for homeostasis and survival. The hypothalamic region at the base of the brain integrates these diverse inputs via the secretion of neuropeptides which are released into a portal system to target the anterior pituitary which regulates reproduction, adrenal function, thyroid function, metabolism and growth. Hypothalamic neuropeptides are also secreted into the general circulation to target end organs such as the kidney (water and electrolyte regulation), uterus (parturition) and breast (lactation). This field, Neuroendocrinology, has yielded important insights into normal and deranged homeostasis in vertebrates and produced a range of billion dollar therapeutics which are widely used in man, companion animals and livestock.

Of the hypothalamic-pituitary-end organ cascades the reproductive system is most exquisitely sensitive to the effects of external and internal environmental regulation as procreation is essential to survival of species and inappropriate reproduction, when nutritional and other conditions are poor, is detrimental to survival of both offspring and mother. A diversity of brain neuropeptides regulate gonadotropins which in turn stimulate the ovary and testis to produce steroid hormones. Steroid hormones control almost all tissues in man and numerous drugs have been developed to decrease steroid input (e.g. for prostatic and breast cancer), or increase input (e.g. hormone replacement therapy and contraceptives). The major regulator of gonadotropins is gonadotropin-releasing-hormone (GnRH). Thus GnRH agonists and antagonists have extensive therapeutic utilisation with annual sales in excess of $2billion. Our group conducts research on GnRH interaction with its cognate GPCR and has developed novel peptide-based analogues which we have taken into the clinic. More recently we have targeted upstream neural regulators of GnRH; Kisspeptin and Neurokin B. These peptides partially regulate GnRH. We have therefore developed antagonists to partially inhibit steroid hormones. Such analogues have application in hormone-dependent diseases such as benign prostatic hyperplasia (afflicting most men of over 50), endometriosis, (10-30% of women) and polycystic ovarian syndrome (up to 30% of women). They also have potential application in novel contraception and postmenopausal flushing. Peptide analogues are seen to have the disadvantage of not being orally active but have advantages in the ability to be formulated as long duration release depot preparations which require infrequent administration and ensure compliance. Peptide analogues also have far fewer off target effects compared with orally-active small molecules.