Regulation of Hormone Gene Expression in Normal and Mutant Rodents

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ABSTRACT

Mutant rodents with specific neuroendocrine defects have been used, in combination with molecular techniques, to study regulatory mechanisms within the mammalian neuroendocrine system. In particular, use has been made of the hypogonadal (*hpg*) mouse and the growth hormone deficient dwarf (*Dw*) rat.

In the male *hpg* mouse, the GnRH agonist Zoladex biased the pituitary towards FSH production as revealed by morphological, protein and mRNA analysis. This investigation also suggested that GnRH may act via at least two secondary messengers, namely PKC and cAMP, which may exert differential effects on glycoprotein hormone subunit gene transcription.

Grafts of normal fetal pre-optic area tissue were delivered to the third cerebral ventricle of female *hpg* mice to investigate the mechanism of gonadal feedback in animals lacking normal neuronal connections. It was found that, in contrast to the male, the female exhibited negative feedback despite the fact that normal neuronal input was disrupted. This suggests that the pituitary may be an important site of negative feedback in the female although it does not exclude feedback effects via oestrogen sensitive interneurons co-transplanted with the graft.

The effects of pharmacological doses of oestrogen upon pituitary hormone gene expression were investigated by Northern blot analysis in the female rat. It was found that, although oestrogen exerted negative feedback on LHβ mRNA levels, it did not appear to inhibit transcription of the gene. The results indicate that oestrogen may regulate LHβ mRNA production by influencing the degree of splicing of the primary transcript.

The above effects were investigated using intronic oligoneuclotide probes. It was found that there was no hybridisation to the transcript corresponding to the mRNA, however, the other precursors were detected. There was more primary transcript in the oestrogen treated animals than in either the ovariectomised or control animals. Female animals were assayed at various stages of the oestrous cycle to investigate the physiological actions of physiological does of oestrogen. Slight elevations in the primary transcript were observed in the animals killed in oestrus, when physiological oestrogen should have been maximal. This may be a mechanism by which oestrogen is able to exert both positive and negative feedback during the oestrous cycle.

The aetiology of the dwarf rat mutation was investigated by a variety of molecular techniques. Preliminary studies indicated that differences were present between the normal and dwarf animals both in the adult and during development in terms of growth hormone gene transcription.