

The role of the full length and splice variant of the ferret LHR in the etiology of spontaneous hyperadrenocorticism in ferrets

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Hyperadrenocorticism is a common disease in neutered pet ferrets, characterized by the excessive production of androgens. The most prominent clinical signs include symmetrical alopecia, vulvar swelling in neutered female ferrets, recurrence of sexual behavior after neutering, and pruritus. Increased concentrations of gonadotropins, which occur after neutering, are thought to have a pivotal role in the formation of these adrenocortical neoplasia. Strong support for this hypothesis is based on the fact that a significant correlation has been found between the age at neutering and age at onset of hyperadrenocorticism. In addition, immunohistochemistry has successfully detected LHRs in the normal and neoplastic adrenal cortex of ferrets. In vivo and in vitro studies have shown that these receptors are only functional in neoplastic tissue.

The current study was set out to determine the full length LHR-sequence in ferrets using conventional PCR and RNA Ligase Mediated Rapid Amplification of cDNA Ends in ferret testes. After elucidation of the full length sequence, the amount of LHR mRNA was measured by real-time RT-PCR, and western blotting was used to determine the amount of LHR protein in healthy and neoplastic ferret adrenal glands. In addition to determining the full length ferret LHR-sequence (fLHR), a major splice variant, skipping exon 9, was detected [fLHR(exon 9)]. Equal amounts of fLHR and fLHR(exon 9) mRNA were detected in healthy adrenal glands. However, in neoplastic adrenal glands the expression of fLHR mRNA was significantly higher in comparison to fLHR(exon 9). With western blotting, no difference in the amount of LHR protein was found between neoplastic and healthy adrenal glands. An hLHR(exon 9) splice variant has also been isolated from a human ovary by others. Studies have shown that this splice variant binds with the full-length hLHR resulting in the inability of binding of hCG. Although most studies in humans have looked into deactivating splice variants of the LHR, the same mechanisms seem to apply for activating LHRs in organs in which the receptor is considered inactive under normal circumstances.

Based on these findings we conclude that although the amount of LHR protein is unaltered during neoplastic transformation, there is a shift in mRNA expression from fLHR(exon 9) in normal adrenal glands to fLHR mRNA in neoplastic ferret adrenal glands. The decreased expression of fLHR(exon 9) may enable gonadotrophins to bind to the ferret LHR and exert a biological effect in ferret adrenocortical tumors.