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Cortisol and progesterone inhibit the transcriptional activity of the LTR region of the Maedi-Visna virus genome

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Maedi-Visna virus (MVV) and Caprine Arthritis Encephalitis virus (CAEV) are the small ruminant lentiviruses (SRLV) which cause chronic mastitis, progressive pneumonia, arthritis and/or encephalitis. Although the infection persists for life, delivery and lactation appear to promote viral expression. Our previous studies, focused on the effect of steroid hormones on Feline Inmunodeficiency Virus (FIV), revealed that viral replication is altered in the presence of estradiol, progesterone and cortisol, which suggests the presence of functional hormone regulatory elements (HRE) sites in the LTR of this virus. Altogether, these findings lead to the hypothesis of whether, like in other retroviral infections, steroid hormones (either sexual such as progesterone and estradiol, or associated to stress such as cortisol) direct the expression of SRLV genes through interaction with HRE located in the promoter/regulatory LTR region of the proviral genome.

The aim of this study was to evaluate the effect of 17ß-estradiol, progesterone and cortisol on the LTR region of the strains EV1 (MVV-like prototype) and 496 (CAEV-like prototype). For this purpose, from each strain the U3-CAP region of both LTRs (which includes the potential regulatory sites of transcription) was cloned into the AcGFP plasmid containing the gen for green fluorescent protein (GFP). A peculiarity of this vector is that it lacks its own promoters, and consequently the expression of GFP depends on the activation of the transcription machinery in the LTR region. Ovine fibroblasts were transfected separately with these two resulting clones and the transcriptional LTR activity was evaluated through the quantification of the GFP expression by flow cytometry, after adding hundred-fold dilutions of each of the hormones in the range between 10^{-3}M and 10^{-13}M, and analyzing the effect after 48 hours. Each experiment was repeated three times.

Cortisol exerted a significant inhibitory effect on the transcriptional activity of the LTR region of both strains at concentrations between 10^{-3}M and 10^{-7}M. Inhibition had a tendency to be higher when using the EV1-derived clone compared to 496-derived clone, but differences were not statistically significant. Progesterone also produced an inhibitory effect at high concentrations (10^{-3}M and 10^{-5}M), similar in both strains. On the contrary, estradiol did not produce any significant effect on any of the derived clones.

These results demonstrate the existence of functional HRE sites located in the U3 region of the LTR of the proviral SRLV genome and may provide an explanation for the cyclic expression of SRLV associated to the reproductive cycle and stress