Analysis of viral transcription and replication in persistently Borna disease virus (BDV) infected cells

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Borna disease virus (BDV) is a neurotropic virus, and causes polioencephalomyelitis in horses and sheep. Recently, it was found that BDV infects a wide range of animal species in natural settings. Further, antibodies to BDV were detected in patients having psychiatric disorders at a significantly higher rate than found in healthy individuals. Therefore, there is growing concern regarding BDV as a potential zoonosis. However, the pathogenicity of BDV has yet to be elucidated such as, the disease process of encephalitis or psychiatric disorders associated with BDV infection. Since BDV is a highly cell-associated virus, few BDV virions are released in infected cell supernatants. BDV does not cause any cytopathic effects in vitro. In addition, it is considered that BDV can persist in animals and humans in vivo. In this study, using MDCK cells which are polarized cells and used as well characterized models of the neuron, we analyzed a mechanism of increased viral transcription and replication in BDV-persistently infected MDCK cells. We established methods to increase viral transcription, and examined agents inhibiting viral transcription.

We found that Ribavirin, EICAR, and RMNPA inhibit BDV transcription and replication. Since these agents have inhibitory effects on viral mRNA cap formation and viral RNA-dependent RNA polymerase, it was elucidated that inhibitors of cap formation and RNA polymerase can be anti-BDV agents. It was indicated that ribavirin has a reversible inhibitory effect on BDV transcription. Therefore, ribavirin may be considered as a candidate anti-BDV drug. BDV transcription and replication were enhanced in confluent MDCK/BDV monolayer cells, by serum starvation, and by actinomycin D treatment, it is thought that the inhibition of cell activities may enhance of BDV transcription. Enhancement of BDV transcription was independent of the inhibition of cellular transcription, inhibition of topoisomerase, expression of p 53, and apoptosis. Treatment with actinomycin D increased the level of BDV transcription, with shifting of the major band of RNA from1.9-kb to 2.3-kb observed. Another intercalating agent such as adriamycin also increase the RNA band shift to 2.3-kb. Moreover, this RNA shifting was also observed in C 6 ／BDV cells. In this study, we evaluated agents for anti-BDV drugs and found enhancement of BDV transcription by actinomycin D and adriamycin.