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Molecular assessment of the potential combination therapy of cytokines with biphalin and AZT for Friend leukemia virus infection *in vitro*

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Abstract:
Biphalin, a dimeric enkephalin analog, is under investigation as a potential, long-lasting medication of pain associated with chronic diseases, like cancer or AIDS. The role of cytokines, and splenocytes in anti-Friend leukemia virus (FLV) activity of biphalin, a synthetic opioid, and AZT was investigated *in vitro*. Mouse splenocytes inhibited FLV replication in *Mus dunni (Dunni)* cells when they were added to the cell culture. This inhibitory effect of splenocytes also was evident when cells were combined with biphalin and AZT as measured using a focus-forming assay. Under cell-free conditions, recombinant interferon gamma (IFNγ), interleukin 2 (IL-2) and IL-4 directly inhibited the FLV reverse transcriptase (RT) activity by 27% to 36%. IFNγ at 0.005 pg to 500 ng inhibited FLV RT activity by 61% to 80%. A combination of 250 ng IFNγ and 50 μg biphalin resulted in a 94% reduction of FLV RT activity, as compared with 61% inhibition by IFNγ alone. The combination of AZT and IFNγ, IL-2 or IL-4 also induced a stronger suppression of FLV RT activity than either cytokine or AZT used alone. In addition, cloned RT from Moloney murine leukemia virus (MMLV) was directly sensitive to inhibition by biphalin. Thus, the anti-FLV effects of splenocytes in combination with biphalin and AZT in cell culture are likely mediated to a large degree by the direct effect of cytokines. This antiviral activity of splenocytes or cytokines combined with chemotherapy, biphalin, and/or AZT, could be used as a complementary therapy to current approaches for retroviral infection and benefit acquired immunodeficiency syndrome (AIDS) patients. In conclusion, biphalin applied primarily as a new medicine for chronic pain treatment in AIDS patients may play a significant beneficial role as a component of antiviral HIV multidrug therapies.

Key words:
biphalin, 3'-azido-3'-deoxythymidine, cytokine, Friend leukemia virus, opioid, retrovirus