INF-β treatment to prolong t-PA treatment window in cerebral ischemia

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Background and Hypothesis: Cerebral ischemia is the 2nd leading cause of death worldwide. The pathological hallmarks of cerebral ischemia are cell damage, degradation of the blood brain barrier (BBB), and inflammation followed by resident microglia activation, peripheral immune cell infiltration and subsequent secondary neurodegeneration. The first line therapy for ischemic stroke is the thrombolytic, tPA. However, only ten percent of patients are eligible for this treatment – primarily due to the risk of cerebral hemorrhage, secondary to BBB breakdown. Less than ten percent of individuals with acute cerebral ischemia are eligible for tPA. The objective of this study is to establish whether matrix metalloproteinase (MMP) activity, implicated in exacerbating the cerebral infarct volume seen with delayed tPA treatment, can be suppressed with Interferon-β (IFN-β) and thus extend the therapeutic window of tPA. **Experimental Design:** We first investigated the therapeutic effect of IFN-β co-administered with t-PA in the mouse model of transient middle cerebral artery occlusion/reperfusion. Second, using immunoblotting technique we investigated the expression levels of MMPs in brain endothelial and microglial cells following various treatment combinations of TNFα and PGE2, t-PA, and INF-β. **Results:** First, we demonstrated that IFN-β co-administered with tPA reduces the infarct size in ischemic brains. Second, we demonstrated in microglial cells that MMP-9 expression induced by TNFα, PGE2, and tPA can be suppressed by IFN-β treatment. Our experiments to demonstrate the expression levels of MMP-3 and MMP-9 in brain endothelial cells require further optimization. **Conclusion and Potential Impact:** Overall these data indicate that IFN-β treatment is a viable therapeutic candidate to suppress the deleterious effects seen in delayed tPA treatment in the setting of acute cerebral ischemia. Furthermore, our preliminary data indicate that the molecular target of IFN-β, in this setting, belong to the MMP family of proteins.