Seminarios internos del IBFG

Effects of different tissue plasminogen activators on the oxidative stress response and neuronal damage, after ischemia-reperfusion injury

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Salón de actos del IBFG

Stroke is one of the leading causes of death and serious long time disability in the world, which makes it a clinically and epidemiologically highly relevant and impactful disease. Intravenous rt-PA (Actilyse®) remains the sole standard treatment for distal vessel occlusions. rt-PA however, offers significant drawbacks, such as the risk of intracranial hemorrhages following treatment, a limited time window for treatment and an increase brain damage upon reperfusion. The main mechanism of damage after reperfusion is the increase in free radical production. Therefore, it is crucial to find new and improved methods of treatment providing greater efficacy as well as decreasing the severity and prevalence of side effects. Tenecteplase (TNK, Metalyse®) is an alternative fibrinolytic drug generated by mutations in three aminoacids of the original alteplase molecule. There is controversy regarding the beneficial effect of TNK *vs* rt-PA in clinical trials with some of them showing a significantly better reperfusion and clinical outcome whilst others demonstrated worse functional outcome.

We wanted to evaluate the effect of TNK vs rt-PA over the toxicity after reperfusion in an *in vitro* model of stroke. We used primary neuronal cultures that underwent an oxygen/glucose deprivation (OGD) protocol to mimic ischemic stroke *in vitro*. We administered rt-PA and TNK at concentration levels similar to those found in brains from stroke patients during fibrinolytic therapy. We assessed the apoptotic neuronal death by flow cytometry and found that rt-PA, induced an increased neuronal toxicity compared to TNK. This effect was corroborated by an increase in caspase-3 activity in the rt-PA treated group compared to TNK. Furthermore, the mitochondrial superoxide anion production was also increased in the rt-PA treated neurons at earlier time points, hinting at a reactive oxygen species (ROS) overproduction by rt-PA as the culprit of the increased neuronal apoptosis under these experimental conditions.

These results show that rt-PA produces an increase in apoptosis during reperfusion compared to TNK. These higher apoptotic levels were, at least in part, induced by ROS overproduction.