

Geldanamycin Induced HSP 70 Expression As A Protective Mechanism Against Stroke

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Abstract

Strong induction of Heat Shock Proteins (HSPs) expression has been demonstrated in many cellular stress environments including heat shock and ischemia. Of those induced in stroke, HSP 70, along with other chaperon proteins, help to restore the structure and function of denatured proteins in ischemic penumbra. Previous *in vitro* studies implicate HSP 90 as the putative cell environment monitoring and stress signal relaying factor that induces HSPs expression through its interactions with Heat Shock factor-1 (HSF-1), a transcription factor for many HSP genes. Increased concentration of denatured proteins in cytoplasm following ischemic events results in dissociation of HSF-1 from HSP 90 via competitive native protein binding with the latter. The dissociation allows monomeric HSF-1 to homo-trimerize thereby dis-inhibiting the suppressed function of HSF-1. Geldanamycin(GA), a benzoquinoid ansamycin, has been shown in both *in vitro* and cell culture studies to mimic the effect of denatured proteins by inducing HSPs expression via HSP 90 binding. In this study, we investigate the *in vivo* effect of GA on HSPs induction using a gerbil ischemia model. Our preliminary western hybridization data indicates GA inducing HSP 70 expression in a dose/time-dependent manner in brains of unstressed gerbils via intraperitoneal injection. Compared to controls, our immuno-staining data on ischemic gerbils with intraperitoneal pre-treatment of GA also shows slight increase in HSP 70 protein expression and less neuronal damage in CA-1 of hippocampus, a functional region in paleocortex that is most sensitive to cerebral ischemic insults. In future studies we plan to repeat the same experiments using intracranial injection of GA to compare the effect of blood-brain-barrier on GA efficacy. Although our data is yet inconclusive, we have so far observed similar effects of GA on HSP 70 expression in *in vivo* models as they were *in vitro*. Should the inductive effect of GA on HSP 70 be confirmed, one could investigate the therapeutic potential of GA in clinical settings. Given the ubiquitous expression of HSP 70 in all organ systems including heart, lung and kidney, one would expect GA to have a broad spectrum of clinical applications.