Hormetic effect of rotenone in primary human fibroblasts.

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Abstract

BACKGROUND: Rotenone inhibits the electron transfer from complex I to ubiquinone, in this way interfering with the electron transport chain in mitochondria. This chain of events induces increased levels of intracellular reactive oxygen species, which in turn can contribute to acceleration of telomere shortening and induction of DNA damage, ultimately resulting in aging. In this study, we investigated the effect of rotenone treatment in human fibroblast strains. RESULTS: For the first time we here describe that rotenone treatment induced a hormetic effect in human fibroblast strains. We identified a number of genes which were commonly differentially regulated due to low dose rotenone treatment in fibroblasts independent of their cell origin. However, these genes were not among the most strongly differentially regulated genes in the fibroblast strains on treatment with rotenone. Thus, if there is a common hormesis regulation, it is superimposed by cell strain specific individual responses. We found the rotenone induced differential regulation of pathways common between the two fibroblast strains, being weaker than the pathways individually regulated in the single fibroblast cell strains. Furthermore, within the common pathways different genes were responsible for this different regulation. Thus, rotenone induced hormesis was related

to a weak pathway signal, superimposed by a stronger individual cellular response, a situation as found for the differentially expressed genes. CONCLUSION: We found that the concept of hormesis also applies to in vitro aging of primary human fibroblasts. However, in depth analysis of the genes as well as the pathways differentially regulated due to rotenone treatment revealed cellular hormesis being related to weak signals which are superimposed by stronger individual cell-internal responses. This would explain that in general hormesis is a small effect. Our data indicate that the observed hormetic phenotype does not result from a specific strong well-defined gene or pathway regulation but from weak common cellular processes induced by low levels of reactive oxygen species. This conclusion also holds when comparing our results with those obtained for C. elegans in which the same low dose rotenone level induced a life span extending, thus hormetic effect.

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