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Toxic effect of resveratrol induced by energy restriction on mitochondrial dysfunction in mouse hepatocytes

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Abstract

Resveratrol (RSV) is a polyphenol classified as a phytoalexin, which occurs naturally and in response to a mechanical injury or biotic and abiotic factors. RSV has been shown to reduce cell viability of pathogenic organisms, probably through inhibition of the electron transport chain (ETC) and F_1F_0-ATPase (which is referred to as oxidative phosphorylation in general), generating a decreased synthesis of energy, causing, in turn, a mitochondrial dysfunction. Interest in RSV has increased in recent years due to the beneficial health effects shown by this stilbene. However, such beneficial effects have been observed only at high concentrations of glucose or lipids, without considering those with adequate or low consumption in which the beneficial effect could be neglected and even show toxic effects. Therefore, the objective of the investigation was to determine whether the amount of glucose modulates the effects of RSV on mitochondrial dysfunction in mouse hepatocytes (Hepa1c1c7). Hepa1c1c7 cells were supplemented with both RSV (0.1 to 1000 μM) and glucose (0.5 to 30 mM). According to the MTT assay, at high concentration of RSV (1000 μM) cell viability significantly decreased by 91% at low glucose concentrations (0.5 to 1 mM), while normal glucose concentration (5 mM) decreased cell viability by 63%, relative to control cells. Furthermore, RSV had no effect on cell

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viability at high glucose concentrations (20 and 30 mM); this indicates that there is a RSV-dependent relationship with the energetic state of the cell. Subsequently, mitochondrial dysfunction was determined using membrane potential, reactive oxygen species (ROS) production, and ADP/ATP ratio. In the ROS production experiment, a decrease in ROS release was observed at the highest glucose concentrations (10, 20 and 30 mM) in cells supplemented with 10, 100 and 1000 μM of RSV, which indicates that RSV inhibits ROS overproduction in a dose-dependent manner, demonstrating its antioxidant effect. Interestingly, under energy restriction concentrations (glucose 0.5 and 1 mM) at concentrations greater than 10 μM of RSV, an increase of ROS release was observed, which corroborates the fact that under restraint energy RSV exerts a toxic effect. Besides, an increase in both mitochondrial membrane potential and ADP/ATP ratio was observed; therefore, it was suggested that RSV is interrupting the flow of electrons, altering the CTE, with a subsequent decrease in ATP production. Altogether, these data support the hypothesis that the toxic effects of RSV are dependent on the cellular energy restriction condition as a result of mitochondrial dysfunction.

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