Sydnone (SYD-1) toxicity in HepG2 cells is Mediated by the Impairment of Mitochondrial Functions

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INTRODUCTION: SYD-1 (3-[4-chloro-3-nitrophenyl]-1,2,3-oxadiazolium-5-olate) has emerging as one potential candidate to treatment of hepatocellular carcinoma. The expressive inhibition of electron transport throughout the respiratory chain in isolated mitochondria was related with its antitumor effect. Noteworthy, in low concentration (25µM), the compound was not cytotoxic for non-tumor hepatocytes, suggesting some selectivity. **OBJECTIVE:** To evaluate the metabolic toxicity of SYD-1 on human liver cancer cells (HepG2) with highlight to mitochondrial bioenergetics. **MATERIAL AND METHODOS:** HepG2 cells were grown in high glucose (HG - 25mM) or galactose (GAL - 10mM) medium that was supplemented with glutamine (4mM to HG and 6mM to GAL), FBS (10%) and penicillin (100U/mL) /streptomycin (100µg/mL). The viability was evaluated by MTT, LDH release and Crystal Violet assays. The respiration was measured by high-resolution respirometry with an Oxygraph-2k (OROBOROS®) in intact cells. The following states of respiration were analyzed: basal (absence of inhibitors or uncouplers), leak (presence of oligomycin) and uncoupled (presence of FCCP). ATP, lactate and pyruvate levels in the supernatant of treated cells were determined using commercial Kits. **RESULTS AND DISCUSSION:** SYD-1 decreased the viability of HepG2 cells grown in HG medium at dose dependent manner and inhibited the basal, leak and uncoupled states of the respiration after 24h of treatment. Decrease in pyruvate levels and increase of lactate levels were observed. Similar but more expressive results were obtained with HepG2 cells grown with GAL medium. ATP levels were reduced only in the supernatants of cells cultured in GAL medium. **CONCLUSION:** These results show that SYD-1 is toxic to HepG2 cells and suggest that its cytotoxicity is related to impairment of mitochondrial metabolism since the effects were more pronounced when oxidative phosphorylation was the preferential pathway for ATP synthesis.

Keywords: mesoionic, SYD-1, HepG2 cells, glucose, galactose, metabolism.
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