64

Enzymatic oxidation of chloramphenicol succinate in human bone marrow and liver

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Chloramphenicol succinate (CAPS) is used orally and IV mainly for treatment of typhoid and meningitis. Its toxicity is generally attributed to disturbances in mitochondrial biogenesis, enzyme and protein synthesis. We hypothesize that CAPS is a substrate for mitochondrial succinate dehydrogenase.

Method: 20 bone marrow samples from Chinese donors were used to study the rate of chloramphenicol (CAP) formation, the effect of a competitive substrate malonate and specific irreversible blocker 3 nitropropionic acid (3NPA). Detection of CAP was carried out by HPLC. Similar experiments were carried out with mitochondria separated from rat liver and human liver (from patients undergoing hepatectomy) by a standard procedure.

Results: In all 20 bone marrow samples, CAPS was oxidized to CAP. The rate of CAP formation without any cofactor was very slow. FAD enhanced the rate of CAP formation and malonate at mM concentrations increased the rate of CAP formation but blocked the reaction at high (0.4-0.8 M) concentrations. 3NPA blocked CAP formation. Human liver and rat liver, mitochondria and homogenate metabolized CAPS to CAP only. In contrast to bone marrow, malonate at low and high concentration increased CAP formation. 3NPA at very low concentrations blocked oxidation of CAPS to CAP and at high concentrations it blocked both oxidation and FAD reduction.

Conclusions: CAPS is a substrate for mitochondrial succinate dehydrogenase, as the metabolism of CAPS is enhanced by FAD and malonate and blocked by 3NPA. In marrow, high malonate concentrations may act in competition with CAPS.

65

Nitroreduction of chloramphenicol succinate in human bone marrow and blood: a possible mechanism responsible for aplastic anaemia.

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Aplastic anaemia is a serious complication of chloramphenicol (CAP) therapy, estimated to occur in 1 in 500 to 10,000 treated patients. It is attributed to topical and parenteral administration of chloramphenicol succinate (CAPS) and may present days, months or years after the initial exposure. Yunis et al postulated that P-NO_2 moiety of CAP was the structural feature underlying the appearance of aplastic anaemia and that highly reactive nitroso (NOCAP) and hydroxylamino (NHOHCAP) metabolites of CAP may be responsible. However, these metabolites have never been identified in humans or animals nor is it established how CAP could be nitroreduced. We postulate that CAPS is a substrate for inducible isoform of succinate dehydrogenease which can oxidize and nitroreduce CAPS.

Method: 100 bone marrow and 20 blood samples were obtained after informed consent from healthy donors. Samples were incubated for 15 min, 1 and 3 hrs at 37^{0}C. After incubation, precipitation and centrifugation, supernatants were injected to HPLC for detection of metabolites.

Results: Marrow and blood samples from only one donor yielded 3 different metabolite peaks (RT 10.5 ± 1, 13.5 ± 1 and 14.5 ± 1). RTs of these peaks were compared with those of standard metabolites. Supernatant from marrow and serum incubated for 15 min. gave 3 peaks with RTs corresponding to CAP, NOCAP and another compound. Blood collected 2 months later yielded no such peaks.

Conclusion: The isoform of succinate dehydrogenase present in marrow and blood of some individuals can oxidize CAPS and can further nitroreduce CAP to NOCAP and another intermediate metabolite (possibly NHOHCAP). In the inital samples, this isoform may have been induced possibly due to Traditional Chinese medicine taken prior to marrow donation.

Yunis et. al. J Lab Clin Med 1980; 96: 36-46.