

# L - ASPARAGINASE - ANTELEUKEMIA AGENT - A REVIEW

Pages with reference to book, From 14 To 17

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This article reviews the most recent developments in the field of biosynthesis and purification of L-asparaginase. The informations about the catabolite repression and metabolism of the enzyme in mycobacteria are reported. The effort of pH and specific antibodies on the catalytic activity of the enzyme have also been described. The enzyme is immobilized on different materials and is used for the treatment of cancer.

L-asparaginase an antileukemia agent has been studied and discussed thoroughly during the recent years (Jabbar and Yaqub, 1976).

L-asparaginase is widely distributed in the biological world (Shnyak et al., 1976; Nefe-lova et al., 1978; Nair et al., 1977).

Kimm et al (1976) isolated L-asparaginase EC-1 and EC-2 from E-COLI.

Sprunke et al (1977) used various acidic and alkaline charcoal and mineral sorbents for the purification of L-asparaginase.

Buka et al (1975) described a method for the determination of L-asparaginase in the presence of NH<sub>4</sub> OH and L-asparagine.

Russell et al (1978) pointed out that the amount of L-asparaginase II in E-COLI wild type strain (cya<sup>+</sup>, Crp<sup>+</sup>) markedly increased the shift from aerobic to anaerobic growth but no increase occurred in a mutant (cya) lacking cyclic AMP synthesis unless supplement with exogenous cyclic AMP.

Netrval (1977) studied the effects of 18 amino and 7 organic acids on the production of L-asparaginase by E-COLI. Pinka (1977) studied the effect of pH on the kinetic parameter of modified asparaginase.

Charlson et al (1978) studied number of cations as moderators of the enzyme.

Maleimide and maleamic acid inhibited the hydrolysis of L-asparagine by L-asparaginase non-competitively as well as competitively (Milman et al., 1978).

Liu et al (1977) observed that enzyme activity was abolished after treatment with dinitro flourobenzene, diazo benzene sulfonic acid, Rose Bengal and tetra-nitro methane.

Shier et al (1976) prepared a conjugate of E. COLI, L-asparaginase and concanavalin A by cross linking with glutaraldehyde and observed that the conjugate may be retained in mouse tissue for longer time than the free enzyme.

Ryoyama (1978) examined the effect of urea on the activity of blood serum L-asparaginase in out bread guinea pigs for comparison between heat resistant and heat sensitive types.

It was found by Kim et al (1975) that L-asparaginase depressed the gastric secretion in rats. Gastric pH was markedly elevated while free acid concentration and total acid concentration were decreased.

Asparaginase collagen membrane completely degraded asparagine in dog blood plasma within 30 minutes by an extracorporeal shunt. Morikawa et al (1978) suggested a chemical application of L-asparaginase in the treatment of neoplasm.

Merkulov et al (1977) noted that L-asparaginase (20 IU/day) administered for 3 days to mice inoculated with friends leukemia virus caused remission of the tumor.

Tamura et al (1978) and Chang et al (1977) described in a review on L-asparaginase a model for enzyme therapy of substrate-dependent tumors.

Block et al (1977) used a number of therapeutic agents including L-asparaginase and found it to be useful for human prostate cancer.

Calich et al (1977) prepared seven rabbit antisera against an L-asparaginase preparation from agonti and found no correlation between the serum protein concentration and antibody activity-

The antilymphoma activity and blood clearance behaviour by the glutaminase free L-asparaginase from VIBRIO SUCCINO-GENES was tested in C3 H mice with transplanted 6 C3 HED lymphosarcoma (Distasio et al., 1977).

Allin and Gnetard (1977) studied the effect of asparaginase and deprivation of some essential amino-acids on nucleic acid and protein-synthesis.

Kung et al (1978) found vincristine prednisone and L-asparaginase in the induction of remission in children with acute lymphoblastic leukemia following relapse.

Two hundred twenty seven children with current acute lymphoblastic leukemia were treated with various combinations of vincristine, prednisone I, cyclophosphamide and L-asparaginase in an approach to the induction of remission. The incidence of remission was 73 per cent. No significant improvement was achieved when cyclo-phosphamide was added to this regimen.

Kondrat et al (1977) studied L-asparaginase sensitivity as asparagine deficiency in 5 tumor cell population i.e. mouse leukemia L-1210, lymphosarcoma L 10-1, lympholeukemia LTL, Burkitts lymphoma and a human ovarian cancer CaO .

E-COLI asparaginase 250-300 (IU/kg) was given i.v. daily upto 3 weeks to patients with systemic malignant disease of the blood (Kondren et al., 1977). Complete remission was observed in 50 per cent of children with lymphoblastic leukemia and 46.1 per cent with acute myeloblasts leukemia.

L-asparaginase has been successfully immobilized in recent years by several methods and used for the treatment of leukemia. These methods included microcapsulation (Chang and Thomas, 1976), immobilization on reconstituted collagen membrane (Olanoff et al., 1975; Jefferies, 1978; Jefferies et al., 1977), gel entrapment with polyacrylamide (O, Driscoll et al., 1975; Updike, 1977; Savage et al., 1976), immobilized on nylon net (Wawro et al., 1976), entrapment in red blood cell (Updike et al., 1976; Sasca et al., 1977), human fibrin (Naito et al., 1977; Inada et al., 1977; Shimizu, 1976).

L-asparaginase from E. COLI A-1 was modified with activated polyethylene glycols (2-o-methoxy polyethylene glycol-4,6 dichloro-s-Triazine) with molecular weight of 750, 100 and 5000. The modification of asparaginase to 73 amino-groups, out of the total 92 amino groups in mole with polyethylene glycol of 5000 daltons gave rise to complete loss of the binding ability towards anti-asparaginase serum from rabbit. This modified asparaginase retained the enzyme activity (7%) and had resistivity against tyrosine and did not show a substantial change of the immunogenic properties (Ashihara et al., 1978).

Nakashima et al (1976) studied the effect of asparagine starvation and L-asparaginase on RNA metabolism in mouse leukemia cells whose growth is independent of asparagine.

Handschi and Robert (1977) described procedures for the synthesis and use of diazo-4-oxo-L-norvaline C as an affinity label for the L-asparaginase active site.

Luecke et al (1978) designed an extracorporeal asparagine filter to be used for decomposition of asparagine in blood by asparaginase.

Dauvarte et al (1978) in a review describe the pharmacological toxicity and antineoplastic effects of asparaginase in the laboratory or in the clinic.

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