[CANCER RESEARCH 36, 1847, May 1976]

Letter to the Editor

Inhibition of Fructose 1,6-Bisphosphatase by 9-β-D-Arabinofuranosyladenine 5'-Monophosphate[1]

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There has been an increased interest in the study of nucleoside analogs as potential therapeutic agents in the treatment of neoplastic diseases (for references, see Ref. 1). The field is also expanding to nucleotide analogs. Among these, ara-AMP[2] has been shown to penetrate animal cells intact and ara-AMP is phosphorylated to the triphosphate (9). 9-β-D-Arabinofuranosyladenine 5'-triphosphate is an inhibitor of mammalian ribonucleotide reductase (6) and DNA polymerase (3). However, it can also be predicted that nucleotide analogs may produce significant effects on enzymes other than those of nucleic acid metabolism. Indeed, 9-β-D-arabinofuranosyladenine 5'-triphosphate has been shown to inhibit also *Escherichia coli* adenyl cyclase (8). This note reports that ara-AMP is, like AMP, an inhibitor of fructose 1,6-bisphosphatase.

Fructose 1,6-bisphosphatase, which catalyzes the hydrolysis of fructose 1,6-bisphosphate to fructose 6-phosphate, is a key enzyme in gluconeogenesis. The enzyme from nearly all sources is strongly inhibited by AMP (10), and this inhibition is considered to be one of the control mechanisms of carbohydrate metabolism (7). The inhibition of fructose 1,6-bisphosphatase by AMP is highly specific, but 2'-deoxyAMP is as inhibitory as 5'-AMP (4, 11). Thus, it appeared *a priori* very likely that ara-AMP would also be an inhibitor of fructose 1,6-bisphosphatase. As shown in Chart 1, ara-AMP proved to be as inhibitory as AMP (K_i of about 20 μM). Thus, if ara-AMP (or other inhibitory AMP analogs) increases the intracellular pool of 5'-nucleotide inhibitors after their administration, this would result in a decrease of the rate of gluconeogenesis. Other close AMP analogs (*i.e.*, the 5'-phosphates of deazaadenosine, formycin, isoadenosine, tubercidin) may also inhibit fructose 1,6-bisphosphatase, thereby altering the regulation of carbohydrate metabolism. Adenine nucleotide analogs could also affect the key regulatory glycolytic enzyme phosphofructokinase, as recently mentioned by Bloch[3] in his studies with tubercidin.

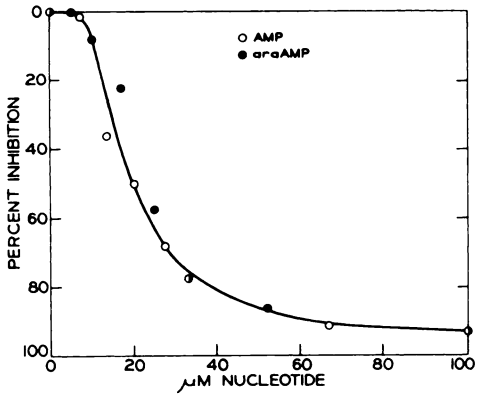

Chart 1. Inhibition of pig kidney fructose 1,6-bisphosphatase by either AMP or ara-AMP. The assays were performed as previously described (5) except for the addition of either AMP or ara-AMP (Sigma Chemical Co., St. Louis, Mo.) at the indicated concentrations. Pig kidney fructose 1,6-bisphosphatase was purified as previously described (2).

ACKNOWLEDGMENTS

I am grateful to Professor Henry A. Lardy for his continued interest and support.

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[1] This work was supported by NIH Research Grant AM 10334 and by American Cancer Society Grant BC 149.

[2] The abbreviation used is: ara-AMP, 9-β-D-arabinofuranosyladenine 5'-monophosphate.

[3] Unpublished data cited on p. 579 of Ref. 1.

Received December 29, 1975; accepted January 21, 1976.