CHAPTER 2

Pyrimidine Nucleosides with Selective Antiviral Activity

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A. Introduction

A high degree of selectivity has now been achieved in experimental viral chemotherapy in both in vitro and in vivo models. A number of “new generation” agents, of which several are pyrimidine nucleosides, can effectively inhibit the replication of herpes simplex viruses with little or no host cell toxicity (Fig. 1). Although the exact mechanisms of action of those compounds may not be fully elucidated, it is clear that their selectivity is dependent on the exploitation of one or more virally specified enzymes. Thus, despite the fact that viruses are obligate parasites, they do code for proteins which are sufficiently different from their host cell counterparts for selective intervention to be possible. In light of the substantial increases in our understanding of the many virally induced enzymes coded for by numerous viruses (KIT 1979), the development of more highly selective antiviral agents seems quite likely.

Even before the advent of these new drugs, it was clear that virus-induced enzymes were important determinants in antiviral therapy (PRUSOFF and GOZ 1973 a). For example, 5-iodo-2'-deoxyuridine (IdUrd), the first agent shown to be effective in an established viral infection in humans (KAUFMAN 1962; KAUFMAN et al. 1962 b), is phosphorylated by the thymidine kinase coded for by herpes simplex viruses. The large increase in activity of this enzyme in virally infected cells and the subsequent intracellular trapping of 5-iodo-2'-deoxyuridine monophosphate (IdUMP) accounts for the selectivity of this drug (PRUSOFF and GOZ 1973 a). Of particular importance, however, is the fact that IdUrd is also a substrate for several host cell enzymes, including thymidine kinase. Thus, metabolic activation and the accompanying cytotoxicity could, and indeed does, occur in normal tissues (CALABRESI et al. 1961). The key difference with respect to the new, highly selective agents is that their interactions with critical virally induced enzymes are highly specific or preferential. They may have little or no interaction with the corresponding host cell enzymes. In some cases, the differences are essentially absolute and the activating reaction is catalyzed only by the virus enzyme (CHEN and PRUSOFF 1979). Thus, an important change in antiviral chemotherapy is that selectivity can now be based on qualitative as well as quantitative exploitation of virus-associated enzymatic activities.

In theory, any virus-specific process could be amenable to chemotherapeutic attack. A number of recent reviews have detailed the potential sites (GOZ and PRUSOFF 1970; MITCHELL 1973; PRUSOFF and WARD 1976; SIDWELL and WITKOWSKI 1979). Depending on the nature of the virus, some or all of the following pro-
cesses could be susceptible to drug intervention: (1) extracellular inactivation; (2) attachment to the host cell; (3) penetration; (4) uncoating; (5) intracellular biosynthetic events; (6) virus assembly; (7) envelopment; and (8) release of mature virus. However, 2-thiouracil, which inhibits viral absorption (STEELE and BLACK 1967), is the only pyrimidine analog known to act at other than an intracellular site. Thus, the virus-associated and induced enzymes involved in nucleoside and nucleotide metabolism, which are the logical targets for these agents, will be emphasized. KIT (1979) in an excellent review, discussed in detail the many enzymes which are known to be virally induced. Numerous investigators have stressed the importance of focusing on these enzymes in the development of selective antiviral agents (PRUSOFF 1967; PRUSOFF and GOZ 1973a; CHENG et al. 1975b; CHENG 1977; COHEN 1977; OXFORD 1977; DE CLERcq and TORRENCE 1978a).

Certain virally induced enzymes catalyze reactions which are unique to the virus-infected cell and are also necessary for viral replication. These enzymes are good targets for selective viral chemotherapy. The RNA transcriptases of influenza and parainfluenza viruses, the RNA replicases of the enteroviruses and rhinoviruses, and the reverse transcriptases of the RNA tumor viruses are examples (see KIT 1979 for review).

Another group of virally induced enzymes catalyze reactions that normally occur in uninfected cells. Often these enzymes are sufficiently different from their host cell counterparts for selective intervention to be possible. As previously mentioned, the thymidine kinase induced by certain of the herpesviruses (KIT and DUBBS 1963) is such an enzyme which has proven susceptible to chemotherapeutic exploitation. The herpes simplex encoded DNA polymerase (KEIR and GOLD 1963) is also in this group of enzymes. The selective antiherpes actions of the phosphonates appear to be mediated through preferential inhibition of the viral polymerase (MAO and ROBISHAW 1975). The high degree of selectivity of the unusual purine analog, acycloguanosine, also results, in part, from interference with the herpes-induced DNA polymerase (ELION et al. 1977; see Chap. 3). The deoxycytidine deaminase (CHAN 1977), DNase (KEIR and GOLD 1963), and ribonucleotide diphosphate reductase (COHEN 1972) activities associated with herpes simplex virus infection provided other possible sites of intervention.

The thymidine kinase induced by herpes simplex virus requires special attention because it is critical for the activity of so many pyrimidine nucleoside analogs (DE CLERcq et al. 1977) and since its multifunctionality and broad substrate specificity have been well characterized. The virus-induced thymidine kinase differs from the host cell enzyme in molecular weight, substrate specificity, electrophoretic mobility, isoelectric point, and immunologic properties (see KIT 1979 for a review). The herpes enzyme has a very broad substrate specificity. It catalyzes the phosphorylation of both deoxythymidine (dTthd) and deoxycytidine (dCyd; JAMIESON et al. 1974; JAMIESON and SUBAK-SHARPE 1974) and interacts with a host of nucleoside analogs (CHENG 1976, 1977; CHENG et al. 1976; FYFE et al. 1978; CHEN and PRUSOFF 1979). The multifunctional properties of this protein have been extended to include thymidylate kinase activity (CHEN and PRUSOFF 1978), a property not shared by the host thymidine kinase. These unique biochemical properties make this enzyme chemotherapeutically exploitable, a fact which will be reiterated in the discussions of the individual agents.