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Review

Suramin: an anticancer drug with unique biological effects

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Introduction

Suramin (Fig. 1) is a hexasulfonated naphthylurea that has been used in the treatment of sleeping sickness and other parasitic diseases for almost 70 years [14]. More recently, suramin was shown to have activity toward human immunodeficiency virus in vitro [26], which led to clinical trials in patients with acquired immunodeficiency syndrome (AIDS). Although suramin treatment resulted in little immunologic improvement, a complete clinical response was observed in a patient with AIDS-associated Kaposi's sarcoma and non-Hodgkin's lymphoma [5]. Subsequent studies have shown that suramin has antitumor activity toward several metastatic cancers refractory to conventional chemotherapy, including renal-cell carcinoma, prostate cancer, ovarian cancer, adrenocortical carcinoma, and certain lymphomas [10, 33]. A variety of toxic side effects have been observed, the most serious of which is a Guillain-Barrè neuropathy syndrome. Optimal antitumor activity has been observed at serum levels above 200 μg/ml, whereas peak levels greater than 300 μg/ml can result in neurotoxicity [10, 33].

For further improvement of the pharmacologic potency, ongoing studies are directed toward (1) optimizing the schedule of suramin administration, (2) the selection of agents that could be used in association with suramin, and (3) the development of suramin analogues with greater antitumor specificity and fewer side effects. However, the incomplete understanding of the drug's primary mechanism(s) of action has so far prevented a rational approach to the last two objectives. In this review, the biological targets of suramin action that might be of therapeutic relevance are discussed.

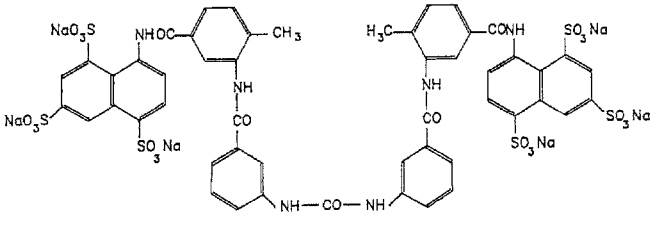

Fig. 1. Structure of suramin

Effects on growth factors and on signal transduction

Suramin has been shown to inhibit the binding of various growth factors to their receptors and to dissociate receptor-bound growth factors. This was generally observed in the concentration range of 50–300 μg/ml. Suramin binds to many different growth factors, such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), basic fibroblast growth factor (FGF), transforming growth factor β (TGF β), and insulin-like growth factor, and antagonizes the ability of these factors to stimulate the growth of tumor cells in tissue culture [1, 6, 16, 17, 30, 35]. Suramin inhibits the biological activity of PDGF by binding to the growth factor rather than to its receptor [16].

The basal rate of guanosine triphosphate (GTP) hydrolysis by GTPases in the membranes of glioma and neuroblastoma cells was inhibited by suramin, the 50% inhibitory concentration (IC_{50}) being close to 30 μg/ml. This was shown to occur via a noncompetitive interaction [3].

At 100 μg/ml, suramin inhibited receptor-stimulated phosphoinositide synthesis in colon-carcinoma cells, most likely due to a direct inhibition of phosphatidylinositol kinase and diacylglycerol kinase. In contrast, suramin concentrations of up to 200 μg/ml had no effect on the basal phospholipid metabolism [22].

Suramin can activate or inhibit protein kinase C (PKC) in a concentration-dependent manner by multiple mechanisms. At low concentrations (below 50 μg/ml), PKC is activated, whereas higher concentrations of suramin lead to inhibition [24]. Type I PKC was about 2 times more sensi-

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tive to suramin inhibition than were types II and III. Interestingly, cyclic adenosine monophosphate (cAMP)-dependent kinase was much less sensitive to suramin, the IC_{50} value being above 1 mg/ml, suggesting differential inhibition of protein kinases by suramin [24].

Nuclear enzymes

Suramin is a potent inhibitor of several nuclear enzymes in vitro, including DNA primase, DNA polymerase α, RNA polymerase, DNA topoisomerase II, and reverse transcriptase, the IC_{50} value being 1–10 μg/ml [2, 9, 19, 29, 32, 34]. The activities of other enzymes such as terminal deoxynucleotidyl transferase and DNA polymerases β and δ were inhibited at 10–150 μg/ml. DNA polymerase γ was very resistant to the inhibitory effect of the drug, the IC_{50} value being more than 400 μg/ml [19, 29, 32].

The inhibition of reverse transcriptase and DNA polymerase was noncompetitive with respect to the deoxynucleotide triphosphate substrate [19, 29, 32], whereas the inhibition of RNA primase was competitive with respect to the ribonucleotide triphosphate substrate [29]. The inhibition with respect to the template may be competitive or noncompetitive, depending on the nature of the template primer [9, 19, 29, 32]. The effects on nuclear enzymes have gained renewed interest following the recent demonstration that suramin enters the nucleus of living fibrosarcoma cells [2]. It has also been shown that suramin interacts with DNA topoisomerase II in the nucleus and that this interaction may play a role in the cytotoxic activity of suramin [2].

Internal membranes and organelles

Suramin enters the cells by endocytosis and becomes concentrated in the lysosomes [21]. This leads to the inhibition of some but not all of the lysosomal enzymes involved in glycosaminoglycan and sphingolipid metabolism, resulting in the accumulation of tissue glycosaminoglycans and sphingolipids [7, 8]. The activities of iduronate sulfatase and β-hexosaminidase were strongly inhibited by suramin in vitro in a non-competitive manner. However, the activites of other lysosomal enzymes isolated from suramin-treated rats were variable and tissue-dependent, and it is possible that a small amount of suramin might actually stimulate the synthesis of some of these enzymes [7, 8].

It has also been suggested that a high lysosomal concentration of polyanions might change the fluidity and fusibility of the lysosomal membranes due to a direct interaction with either lipid and/or polypeptide moieties of the membrane [20].

Suramin has been reported to inhibit various ion pumps through inhibition of adenosine triphosphatase (ATPase) activity. These include the Na^+-/K^+-activated transport system in red-blood-cell ghosts, the Ca^{2+} pump in the sarcoplasmic reticulum, and vacuolar H^+-ATPase [13, 23, 27].

Suramin inhibited the adenosine diphosphate (ADP)-stimulated respiration in intact mitochondria, possibly as a result of inhibition of ADP transport into the mitochondrion [4]. Suramin has also been reported to disrupt the cellular energy balance and respiration in prostatic carcinoma cells at concentrations starting at 150 μg/ml [31].

Cell adhesion and migration

Suramin appears to have a direct as well as an indirect effect on cell adhesion and migration. Melanoma-derived heparanase, an endoglycuronidase that plays an important role in metastatic melanoma-cell invasion through basement membranes, was totally inhibited by suramin at 150 μg/ml [28]. Suramin was also capable of preventing the interaction of melanoma cells with laminin or thrombospondin in the extracellular matrix, thereby inhibiting their adhesion and migration [36]. Finally, suramin appears to have antiangiogenesis activity, that is, the ability to impede the development of new blood vessels essential for tumor growth and invasion [18].

Continued exposure to suramin has been shown to affect glycosaminoglycan metabolism in patients, which may lead to elevations in circulating heparan and dermatan sulfate [25]. Given the importance of glycosaminoglycans in metastasis and tumor angiogenesis, this might represent an alternative reason for suramin's anticancer activity.

Differentiation

At 100 μg/ml, suramin inhibited the growth of human colic adenocarcinoma cells in culture and induced their differentiation into enterocyte-like cells. The differentiation was fully reversible once the drug had been removed from the culture medium [11]. Suramin was also capable of inducing a partial differentiation of mouse neuroblastoma cells and rat glioma cells [12, 15].

Conclusion and perspectives

At present the primary mechanism(s) of suramin action is not known. It is possible that several of the factors mentioned in this review are of importance for the drug's antitumor activity and even that different mechanisms are of importance for different cell types. An improved knowledge about the relative importance of the many different biologic effects of suramin is essential to the establishment of better drug combinations and to the development of suramin derivatives with an improved therapeutic index. The development and characterization of suramin-resistant cells would be a major step in this direction.

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