Poliaminas no câncer. Inibidores seletivos das poliaminas e da ornitina decarboxilase. Trinta e sete anos de experiência (2010)


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Abstract

As soon as the natural polyamines (PAs), putrescine (Put), spermidine (Spd) and spermine (Spm), were recognized as ubiquitous constituents of eukaryotic cells, their involvement in growth-related processes attracted particular interest. The high activities of ornithine decarboxylase (ODC) and S-adenosylmethionine decarboxylase (AdoMetDC) in rapidly growing tissues and cells, particularly in tumour cells, suggested PA biosynthesis as a target for antineoplastic therapy. In the course of the years selective inhibitors have been developed for literally all enzymes of PA metabolism. Some became important as tools in the elucidation of the PA metabolic system, but only few of them were efficient as inhibitors of tumour growth. A major reason for the inefficacy of selective enzyme inhibitors as anticancer drugs is the sophistication of the system, which regulates intracellular PA pools. Selective blockade of a single enzyme induces changes of metabolism and transport, which compensate for the deficit. The selective impairment of tumour growth is in addition hampered by the ubiquitous occurrence of the PAs, their importance in normal functions of nearly all mammalian cells, and the ability of the mammalian organism to utilize exogenous (gastrointestinal) PAs. Among the inhibitors of PA-related enzymes, the ODC inactivator (R, S)-2,3-difluoromethyl)ornithine (DFMO) became most famous. Although it was disappointing in most therapeutic attempts to use it as single drug, it has--based on its low toxicity--considerable potential in cancer chemoprevention, and it turned out to be a highly efficient anti-trypanosome agent. Very likely DFMO is suitable to improve the efficacy of some of the current cytotoxic drugs, and it may allow one to create new therapies in combination with other PA-directed drugs. Some of the less selective enzyme inhibitors, particularly those, which inhibit two or more enzymes of PA metabolism, appear to have had a chance to become practically useful, but they have not been developed energetically. Disregarding DFMO, the AdoMetDC inhibitor SAM486A is the only compound for which clinical trials were published. The future of this drug is unclear at present; presumably phase III clinical trials have been discontinued. One of the lessons that had to be learned from the work on selective enzyme inhibitors was that PA metabolism is a much more difficult target, than has been expected on the basis of the simplicity of the PA structures, and the simple reactions involved in their biosynthesis. In order to inhibit tumour growth several reactions or regulatory functions of PA metabolism have to be impaired at the same time. Recent efforts devoted to the development new types of anticancer drugs, which are based on the perturbation of PA metabolism by structural analogues of the natural PAs, take this message into account. These approaches are the topic of the 2nd part of this overview.

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Abstract

Owing to their role in growth-related processes the natural polyamines (PAs), putrescine (Put), spermidine (Spd) and spermine (Spm), were identified about 30 years ago as potential targets for the development of anticancer drugs. It was presumed that inhibition of a key enzyme of PA biosynthesis, followed by the depletion of the intracellular PA pools results in the prevention of cell growth. Initial efforts were nearly exclusively focused on the design and synthesis of selective inhibitors of the PA biosynthetic enzymes. This period is reviewed in the 1st part. Selective inhibition of ODC caused in various cell lines growth inhibition, but was usually not sufficient to inhibit tumour growth, because the PA regulatory system outbalances selective enzyme blockade by enhancing compensatory reactions, and because exogenous PAs are used if de nova synthesis is impaired. When these facts were recognized, new targets were envisaged. Among these the PA uptake system and the deregulation of PA homeostasis became most attractive. They are the major topic of the present 2nd part. Inhibition of PA uptake from the cellular environment is expected to improve the efficacy of drugs, which rely on the depletion of intracellular PA pools. During the past few years several potent inhibitors of the PA uptake system became known. However, more work will be needed to allow their assessment as anticancer drugs in combination with DFMO and other compounds capable of depleting PA pools. The PA transport system also offers the possibility to improve the accumulation by tumors of compounds, which are tethered to PA structures. This can be achieved for the following reasons: (a) Structural requirements of the PA uptake systems are not stringent. (b) Tumour cells accumulate PAs more avidly than most non-transformed cells. (c) The transport rate for PAs is higher in cells with depleted PA pools, than in cells with a normal PA content. (d) In cells, which proliferate rapidly, PA depletion by biosynthesis inhibitors is more effective, than in slowly growing cells. The most actively pursued approach is currently based on the inhibition of tumour growth by cytotoxic structural analogues of the natural PAs. Some of these compounds mimic regulatory properties of the natural PAs. If a PA mimic accumulates in cells, it induces catabolic processes, suppresses biosynthetic reactions, and depletes the pools of Put, Spd and Spm. N1,N11-bis(ethyl)norspermine is a prototype of the PA mimetics. During the last decade a very large number of PA derivatives and structural analogues have been prepared, which are capable of inhibiting cell growth at low micROM concentrations. Among the new PA-like structures several compounds were identified, which prevent cells from growing, without depleting PA pools to an extent that would be necessary to prevent cell growth. They may be considered as PA antagonists, although their mode of action is not well understood. A therapeutically useful drug has not yet been identified among the PA analogues. In many instances investigations were stopped at a preliminary stage. Recently synthesized compounds have not yet been pursued far enough to justify the initiation of clinical trials. Only very few toxicological results of the new structures have been reported, although the knowledge of the toxicology of Spm analogues is of eminent importance. PAs are ubiquitous cell constituents and are indispensable for normal cell function. However, extracellular PAs, and particularly extracellular Spm is cytotoxic and neurotoxic. These properties are shared by close structural analogues. A major difficulty in the development of PA analogues to therapeutically...
useful drugs is, therefore, the identification of structures, which do not share neurotoxic properties with Spm. Several tetramines are presently in early phases of clinical trials. It will be a matter of a few more years to allow one to decide, whether PA-related approaches of cancer therapy are a success or a failure.

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