Introduction

The cytoskeleton of eukaryotic cells is a filamentous network formed by microtubules, microfilaments and intermediate filaments. The cytoskeletal network is responsible for the mechanical properties of the cell that modulate functions such as cell shape, locomotion, cytokinesis, and translocation of organelles. Experimental evidence suggests that there are many important functions of dynamic cytoskeletal network besides the regulation of cellular mechanics. The cytoskeleton also provides connections between cellular structures and presents a large surface area for interactions of various proteins and signaling molecules. Modulation of cytoskeletal network may influence cell signaling, ion channels and intracellular calcium levels. The reorganization or degradation of all cytoskeletal filaments is associated with apoptosis. Cytoskeleton is thus essential for regulation of cellular functions, cell integrity, and viability. The relationships between direct mechanical effects of modulations of cytoskeletal structures and cellular functions remains to be elucidated.

The aim of this minireview is to characterize the most important compounds of natural origin which interact with microtubules. Microtubules are tubulin polymers involved in many cellular functions (10), one of which being the formation of the mitotic spindle required for chromosome moving to the poles of the new forming cells during cell division (2). The importance of microtubules to cellular functions and the use of them is one of the most frequent therapeutic strategies for carcinoma treatment. The survey of the most important natural microtubule inhibitors is summarized in this paper.

Microtubule system

Tubulin is a protein whose quaternary structure is composed of two polypeptide subunits, α- and β-tubulin. Several isotypes have been described for each subunit in higher eucaryots. Microtubule functions are based on their capacity to polymerize and to depolymerize. This process is a very dynamic and is attended with rapid shortening or elongation of the cell structures. Tubulin is a GTP-binding protein and the binding of this nucleotide to the protein is required for microtubule polymerization, whereas the hydrolysis of the GTP bound to polymerized tubulin is required for microtubule depolymerization. Microtubule stability in healthy cell is regulated by the presence of some proteins called microtubule-associated proteins (MAP) which facilitate microtubule stabilization. The cellular mechanisms regulating microtubule assembly is highly sensitive to the concentration of Ca²⁺. The low cytosolic Ca²⁺ level characteristic of the resting state of most eucaryotic cells promotes microtubule assembly, while the localized increase in Ca²⁺ cause microtubule disassembly (13). Microtubules forms through polymerization of protein dimers, consisting of one molecule each of α- and β-tubulin. Dimer and polymer are in a state of dynamic equilibrium, so that the network can respond flexibly and quickly to functional requirements. The polymer forms a fine, unbranched cylinder, usually with internal and external diameters of 14 and 28 nm, respectively.
Several unfavorable characteristics have been observed for vincristine and epothilone A and B, among others due to the toxicity of the molecules. Several disadvantages have been indicated for application of these compounds to chemotherapy. The binding of colchicine to tubulin becomes faster and reversible when a methyl group replaces the acetyl group present on the amine of the B ring, yielding the compound known as colcemide.

On the same site as colchicine bind also podophyllotoxin, plant compounds obtained from Podophyllum peltatum. Podophyllotoxin is a tetracyclic compound with four rings A, B, C, and D, linked to an aromatic ring with three methoxy groups. This alkaloid is, like colchicine, a drug that prevents microtubule polymerization. It has been used for topical treatment of some benign skin tumors. Some synthetic derivatives of podophyllotoxin appear to be more active than podophyllotoxin alone in the treatment of leukemias and solid tumors.

### Microtubule-stabilizing compounds

Among these compounds, the best known one is taxol (paclitaxel), tetra cyclic compound obtained from the bark of the Pacific yew (Taxus brevifolia). In the structure of taxol there are two aromatic rings and a tetracyclic-structure containing an oxetane ring which is required for the activity of the drug (18). The primary action of this compound is to stabilize microtubules, preventing their depolymerization. In this way taxol will block proliferating cells between G2 and mitosis, during the cell cycle. The binding of taxol appears to occur at different localizations at the amino- and carboxyl-terminal regions (35). Halichondrin B, the most known compound with such mechanism as vinblastine (4,41). From the fungus Rhizopus chinensis was isolated other cytotoxic macroline containing an oxetane ring and with potential activity in several murine and human tumor models (6). Cryptophycin A is a new antimicrotubule agent, active against some drug-resistant cells (44) and with potent antiproliferative effect and with excellent antitumor activity against mammary, colon, and pancreatic adenocarcinomas (33). A highly cytotoxic macroline lactone polyether has been isolated from a Spongia species with potent activity in several murine and human tumor models (6). Cryptophycin A is a new antimicrotubule agent, active against some drug-resistant cells (44).

### Compounds with disorganization effect on microtubule network

Some natural marine compounds with anti-tumoral activity were found to disorganise the microtubule network (12). There are eutectinium 743, tetracyclodisoxonine alkaloid isolated from the marine ascidian, Eutextudina turbata, (15,24), several families of the magnoliaceae, for example lamarinol Q, parylene alkaloids iso lated form marine tunicates belonging to the genus Didemnum (36), as well as cyclic depsipeptides of the family idemnins (31). Didemmins were isolated from the marine tunicates Tridemnum solidum and Apylida alba (47) and many very biologically active compounds of this family were prepared also synthetically or semisynthetically (40).

**Microtubule-structures**

- **Dolabella auricularia**
- **Maytana serpyllifolia**
- **Tridemnum solidum**
- **Dolabella auricularia**
- **Eutextudina turbata**
- **Cryptophycin A**
- **Podophyllotoxin**
- **Vinblastine**
- **Vincristine**

Additional details are provided in the text.
ly, the so called microtubule (Fig. 1) (22). Assembly is initi-
ated by the binding together of α, β dimers to form short proto-
filaments, 13 of which subsequently arrange them-
seled by side to form the microtubule. Subsequent growth of the
microtubule is polar, occurring mainly at the so-called plus end of the
protofilaments through the addition of fur-
ther dimers. Addition involves GTP, which is bound to the di-
meter, being cleaved to GDP, which remains attached to the
tubulin. The binding site for GTP is on the β-subunit. When
the cell becomes enriched with GTP, tubulin dimers, hydro-
lysis to GDP, tubulin falls behind the rate of assembly and an
α, β-tubulin-GTP cap forms at the plus end of the protofila-
ments blocking further growth of the microtubule.

Catharanthus roseus, a plant from warm climate. The most
important compounds of this group are vinblastine and
vincristine, compounds composed from a tetracyclic struc-
ture of catharanthine and a pentacyclic structure of vindoli-
ne (41). Both structures appear to be important for both
vinblastine and vincristine activity. The analysis of the loca-
zation of vinblastine-binding site on tubulin has indicated
that it occurs at the central region of the beta-tubulin subu-
net (37). In this region is also GTP binding site and it has been
shown that vinblastine and other related mole-
cules can prevent the binding of GTP to tubulin. Vinblastine
is mainly useful for treating lymphocytic and histiocytic
lymphoma, Hodgkin’s disease, Kaposis’s sarcoma, and advan-
ced breast or testicular cancer. Vincristine is used mainly to
reat acute leukemia, neuroblastoma, rhabdomyosarcoma,
Hodkin’s disease and other lymphomas. Semisynthetic de-
rivatives of vinca-alkaloids with lower toxicity are now at
different phases of clinical trial, e.g. form vincristine or vi-
norulin, which are tested in breast cancer. Other microtu-
bule inhibitors are dolastatin isolated from the sea hare
(Dolabella auriculata), compound with both pyridoline and
thiazoline moiety in the molecule. griselobin, an anti-
biotic produced by Psilocybin griseofulvin, maytansine,
a macroclide compound from rainforest plant Manotum ser-
atus and others family Cecalistraceae (34), famous ethnomed-
dicine known in western Amazonia as chuchuma.

Halichondrin B is the most potent member of a class
of polyether macrolides isolated in low yield from four dif-
ferent sponge genera - Asthenia, Halichondra, Lissodendoryx,
and Boulderia, but binding to the middle region of
a alpha-tubulin has already been reported (28). Taxol has
been used mainly for the treatment of breast and ovarian
cancer but also it has been tested for other types of tumors
such as lung cancer, head and neck cancer and melanoma.
Several disadvantages have been indicated for application
of this very actual anti-cancer compound. One of them,
the relative low amount that can be obtained from the bark of
the Pacific yew (Taxus brevifolia). In the structure of ta-
sol there are two aromatic rings and a tetracyclic-structure
containing an oxetane ring which is required for the activi-
ty of the drug (18). The primary action of this compound is
to stabilize microtubules, preventing their depolymerizati-
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en G2, and mitosis, during the cell cycle. The binding of
taxol appears to occur at different localizations at the ami-
no terminal, tyrosine and serine residues (35). Halichondrin B
is the most known compound of this family, as well as cyclic depsipeptides of the fami-
lies - dolastatin, maytansine, dolastatin, and many very biologically active compounds of this family
were prepared also synthetically or semisynthetically (40).

Several disadvantages have been indicated for application
of this very actual anti-cancer compound. One of them,
the relative low amount that can be obtained from the bark of
the Pacific yew and its relatively rare incidence restrict to
the forests of the Pacific Northwest of the USA and
Canada. This problem has been partially solved by re-
ci-synthesis of this compound (32). Another disadvantage
is the low solubility of taxol in water, thus, this drug
must be dispersed and dissolved in oil and this solvent could effect to
cardiac functions or promote allergic reactions. Also, this
problem has been partially solved by synthesising some ta-

tol analogs with a higher solubility in water (32).

Dolactolin is the most potent member of this family and its
disclosed to be a very effective antitumor compound. Its ac-
tion is the discovery of the marine-derived
dolastatin, whose anti-miotic mecha-
nism of action includes the polymerization and stabilizati-
on of microtubules in a method analogous to that observed
with the structurally unrelated compound taxol (29,30).

4. Compounds with disorganization effect
on microtubule network

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(12). There are eteicinamide 743, tetrahydroxinosoline
alkaloid isolated from the marine ascidian, Eutheca
burtii, (15,24), several members of the family of lan-
elarinus, for example lamalin A, 30% subaromatic alkaloids iso-
lated from marine tunicates and many other very biologically active compounds of this family
were prepared also synthetically or semisynthetically (40).

The classification of microtubule
natural inhibitors

Microtubule inhibitors represents chemically very varie-
gated group of compounds from different biological sour-
ces with strong effect on cytoskeletal functions and strong
toxicity. Microtubule functions in cell depend on the capa-
city of tubulin to polymerize or the capacity of microtubu-
les to depolymerize.

Compounds which are able to influence these processes,
i.e. microtubule inhibitors (also anti-tubulin agents, anti-
totic agents, etc.), can be divided into four group according
to their mechanism of action. 1. Compounds which bind to
GTP site, 2. compounds which bind to colchicine site, 3. compounds which influence as microtubule-stabilizing
agents, and 4. compounds which do microtubule network disorganization.

1. Compounds bind to GTP site

Typical representatives of this group of microtubule po-
soms are vinca alkaloids, compounds derived from

Fig. 1. The structure of microtubule polymer cylinder, usu-
ally with internal and external diameters of 14 and 28 nm,
respectively.
Applications of microtubule inhibitors in future research

There are many demonstrations that mechanical forces mediated by cytoskeleton play a vital role in assembling cellular structures. Moreover, recent experimental evidence demonstrates the multiple interactions between cytoskeletal structures and ion channels, calcium fluxes, and events connected with signal transduction. The process of microtubule assembly proceeds in a cell-free system and the effects of various inhibitors can be thus studied even in the test tube. The use of various natural microtubule inhibitors provides the possibility to study the mechanisms of assembly and disassembly of cytoskeletal structures as well as the role of cytoskeleton in spatial and temporal integration of vital cell functions.

The regulation of microtubule assembly depends on the ability of tubulin heterodimers to bind GTP. The GTP bound to the β-polypeptide is hydrolyzed to GDP plus phosphate (26). The course of assembly and disassembly of microtubules is therefore affected by the action of GTPases. A number of heterotrimetric GTPases or small GTPases of the rho family move on the cytoskeleton after cell activation (9,46). Moreover, a direct transfer of GTP from tubulin to the α subunit of the Gs and Gi protein has been reported (39). On the other hand it has been reported that microtubules can also assemble in the presence of non-hydrolyzable GTP analogues. These observations may demonstrate that such interactions do not entirely serve to microtubule reorganization, but may be also related with cell signaling pathways. The use of various microtubule inhibitors which bind to GTP site could contribute to the study of this suggested role of microtubules in eucaryotic cells.

Polymerization of tubulin heterodimers is regulated by Ca2+ concentration. Under low Ca2+ concentration the cytoplasm of most eucaryotic cells, much of the tubulin is assembled into microtubules. Localized increases in Ca2+ concentration cause microtubule disassembly (13). The alteration of microtubule structure by colchicine has been reported to enhance the activity of Ca2+ channels in Lymnaea neurons and mammalian hippocampal pyramidal neurons (25). An intact microtubule system is required for the IP3-dependent Ca2+ release from intracellular stores (17). The inhibitory effect of colchicine in saponin-permeabilized platelets has been reported (8). Disruption of microtubules by colchicine has been reported to increase conductance of calcium channels in skeletal muscle (21), and decreased conductance of snake twitch fibre end plates (20). The mechanism of this functional change and the role of cytoskeletal structures in the transmembrane ion transport is not known. On the other hand, taxol had no effect on the ion channels in hippocampal neurons (38).

Disruption of microtubule function by taxol leads to increased phosphorylation and to the cell death (7,16). Degradation of tubulin can occur very early in the course of apoptosis. It has been reported in neuronal cells treated with glutamate (1). Although the relation between the microtubule system and the apoptotic program remains unclear, the disruption of microtubule turnover undoubtedly leads to cell death.

Conclusions

Microtubule inhibitors from different natural sources represents chemically very variegated group of compounds with strong effect on cytoskeletal function and cell toxicity. The use of this poison is one of the most frequent therapeutic strategies for carcinoma treatment. Drugs like vinblastine and taxol have wide clinical use, although they have some drawbacks. The discovery of new compounds such as epothilones, halichondrins, didemmins, etc., could overcome some of the problems found with the use of the earlier drugs. In addition, already some these natural toxic compounds are used as outstanding scientific tools in biological experiments and serve the purpose of model structures for synthesis new compounds with expected effect.

We would like to thank Miss Katerina Svitkova from the Institute of Chemical Technology, Prague, for technical assistance.

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References

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Chemical structures of the oximes used against OP poisoning have been extensively studied as they play a role in the reactivation of acetylcholine (ACh) and oxime reactivators to reverse respiratory failure from excessive airway secretions, confusion, hypotension, and hypothermia (1-3). Death from exposure to OP compounds is generally due to respiratory failure (5,6). The clinical signs include salivation, diarrhea, stimulation of the CNS, mydriasis, and convulsions (5,7). OPIs induce clinical signs including salivation, diarrhea, vomiting, seizures, and even respiratory failure (5,7). One of the most toxic OPIs, mevinphos (2-methoxycarbonyl-1-methylvinyl dimethylphosphate), is used for its high efficacy against various insect species (4). The 24h intra-bonyl-1-methylvinyl dimethylphosphate), is used for its high rate of biodegradation. They are also used in large quantities in agricultural fields (1,15). In spite of relatively low toxicity in comparison with highly toxic nerve agents, they have passed occupational hazards to workers employed in the application of these compounds. Carcinogenic and neurotoxic effects of OPs are well-recognized (3,5). The choice of OPI in agricultural fields has replaced more resistant chlorinated hydrocarbon compounds. The choice of OPI is also influenced by the willingness to the resistance of OPI in agricultural fields has replaced more resistant chlorinated hydrocarbon compounds. The choice of OPI is also influenced by the resistance to various invertebrates, the efficacy against highly toxic polyaryl phospha (14), and in vitro studies. Transplantation 1991;52:656-61.

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Summary: The increased international concern about the possible occupational hazards to workers employed in the application of OPI has prompted us to critically consider the expected value of currently available antidotal treatment of OPI poisoning. Unfortunately, none of currently available oximes can be regarded as a broad spectrum antidote (18). Although the bispyridinium oxime HI-6 (Figure 1) is considered to be the most efficacious oxime against highly toxic OP compounds, the bispyridinium oxime HI-6 was evaluated in combination with benactyzine against acute poisoning with the organophosphorus insecticide mevinphos in mice. 2. When mice were treated two min after mevinphos poisoning, no significant differences in their therapeutic effectiveness of tested oximes were observed. They increased the 24h LD50 values of mevinphos approximately three times in comparison with non-treated intoxicated animals. 3. On the other hand, there were significant differences in their therapeutic efficacy when they were administered 30 sec following mevinphos challenge. The monopyridinium oxime 2,5-PAEtM seems to be the most efficacious against mevinphos toxicity. 4. Use of new monopyridinium oxime and acetylcholine receptor recovery. Br J Pharmacol 1997;122:240-42.

One of the most toxic OPI, mevinphos (2-methoxycarbonyl-1-methylvinyl dimethylphosphate), is used for its high efficacy against various insect species (4). The 24h intramuscular (i.m.) LD50 of mevinphos for mice is 0.79 mg/kg body weight (38).

OPI induce clinical signs including salivation, diarrhea, lacrimation, tremors, convulsions and respiratory distress. Death from exposure to OPI compounds is generally due to respiratory failure from excessive airway secretions, construction of the airways and a loss of central respiratory control (13). Antidotal treatment of poisoning with OPI usually consists of anticholinergic drugs to counteract the accumulation of acetylcholine (ACh) and oxime reactivators to re-activate OPI-inhibited acetylcholinesterase (EC 3.1.1.7) (3).

Fig. 1: Chemical structures of the oximes used

Original Article

A COMPARISON OF THE EFFICACY OF NEW MONOPYRIDINIUM OXIMES WITH THE OXIME HI-6 AGAINST MEVINPHOS IN MICE

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Introduction

Organophosphorus insecticides (OPI) have become the most widely used class of insecticides in the world. The use of OPI in agricultural fields has replaced more resistant chlorinated hydrocarbon compounds. The choice of OPI is based on their properties of low bioaccumulation and high rate of biodegradation. They are also used in large quantities because of their high potential for insect knockdown capability (15). In spite of relatively low toxicity in comparison with highly toxic nerve agents, they have passed occupational hazards to workers employed in the application of these compounds. Carcinogenic and neurotoxic effects of OPI are well-recognized (3,5). The choice of OPI in agricultural fields has replaced more resistant chlorinated hydrocarbon compounds. The choice of OPI is also influenced by the resistance to various invertebrates, the efficacy against highly toxic polyaryl phosphates (14), and in vitro studies. Transplantation 1991;52:656-61.

27. Kowalski RJ, Giannakakon P, Hamel E. Activities of the microtubule stabilizing bispyridinium oxime HI-6 was evaluated in combination with benactyzine against acute poisoning with the organophosphorus insecticide mevinphos in mice. 2. When mice were treated two min after mevinphos poisoning, no significant differences in their therapeutic effectiveness of tested oximes were observed. They increased the 24h LD50 values of mevinphos approximately three times in comparison with non-treated intoxicated animals. 3. On the other hand, there were significant differences in their therapeutic efficacy when they were administered 30 sec following mevinphos challenge. The monopyridinium oxime 2,5-PAEtM seems to be the most efficacious against mevinphos toxicity. 4. Use of new monopyridinium oxime and acetylcholine receptor recovery. Br J Pharmacol 1997;122:240-42.

Summary: The increased international concern about the possible occupational hazards to workers employed in the application of OPI has prompted us to critically consider the expected value of currently available antidotal treatment of OPI poisoning. Unfortunately, none of currently available oximes can be regarded as a broad spectrum antidote (18). Although the bispyridinium oxime HI-6 (Figure 1) is considered to be the most efficacious oxime against highly toxic OP compounds, the bispyridinium oxime HI-6 was evaluated in combination with benactyzine against acute poisoning with the organophosphorus insecticide mevinphos in mice. 2. When mice were treated two min after mevinphos poisoning, no significant differences in their therapeutic effectiveness of tested oximes were observed. They increased the 24h LD50 values of mevinphos approximately three times in comparison with non-treated intoxicated animals. 3. On the other hand, there were significant differences in their therapeutic efficacy when they were administered 30 sec following mevinphos challenge. The monopyridinium oxime 2,5-PAEtM seems to be the most efficacious against mevinphos toxicity. 4. Use of new monopyridinium oxime and acetylcholine receptor recovery. Br J Pharmacol 1997;122:240-42.

One of the most toxic OPI, mevinphos (2-methoxycarbonyl-1-methylvinyl dimethylphosphate), is used for its high efficacy against various insect species (4). The 24h intramuscular (i.m.) LD50 of mevinphos for mice is 0.79 mg/kg body weight (38).

OPI induce clinical signs including salivation, diarrhea, lacrimation, tremors, convulsions and respiratory distress. Death from exposure to OPI compounds is generally due to respiratory failure from excessive airway secretions, construction of the airways and a loss of central respiratory control (13). Antidotal treatment of poisoning with OPI usually consists of anticholinergic drugs to counteract the accumulation of acetylcholine (ACh) and oxime reactivators to re-activate OPI-inhibited acetylcholinesterase (EC 3.1.1.7) (3).

Fig. 1: Chemical structures of the oximes used

Key words: Mevinphos, Monopyridinium oximes, HI-6; Benactyzine, LD50; Mouse;