Introduction

The polyamines, putrescine, cadaverine, agmatine, spermidine, and spermine, are low-molecular weight substances, synthesized in eukaryotic cells from their immediate precursors, ornithine, lysine, or arginine. Their chemical structures are given in Fig. 1.

These nitrogenous compounds are essential for growth. An animal’s endogenous supply of these metabolites derives from biosynthesis, the diet, or by synthesis in the intestinal flora. The polyamines are found in fruits and vegetables, many foods of animal origin (milk, eggs, fish, and meat), and fermented food products (cheese, beer, and sauerkraut). Being nitrogenated compounds, they are considered as “minor” components of the diet. Ornithine decarboxylase (ODC), an enzyme of short half-life, is the rate-limiting catalyst for biosynthesis of putrescine, spermidine, and spermine. The relevant biochemical pathway is schematically displayed in Fig. 2. In some cells, this enzyme is phosphorylated by a protein kinase reaction that is dependent on spermidine and spermine. Putrescine antagonizes the phosphorylation (7).

Cellular polyamines are found in free or complexed forms, the latter made possible, above all, by the presence of positive charges at their protonated nitrogen atoms. Their particular structure facilitates interaction with anions and binding to nuclear and membrane structures, particularly phospholipids, proteins, and DNA. The natural polyamines, spermine and spermidine, their biosynthetic precursor putrescine, and their analogue cadaverine derived from lysine, stimulate GTPase activity (1). Mammalian requirements for these substances are elevated during phy-
and cultured cells, it was found that an early rise in the level of putrescine is important for hormonal and/or agonist stimulation of DNA synthesis (16). Putrescine binding to nuclear macromolecules has been proposed to modulate DNA synthesis and transcription. In many experimental cell systems, the polyamines sometimes act synergistically or antagonistically, making it difficult to distinguish their individual effects. Polyamines, spermine, spermidine, and putrescine, all exhibit antimutagenic potential against ethyl methanesulfonate (EMS)-induced effects on MAO. In addition, spermidine and putrescine demonstrate potential to reduce the number of spontaneous revertants in modified Ames tests (17). The loss of feedback regulation of the polyamine transport system is sufficient to induce apoptosis (29).

**Cadaverine**

Cadaverine (1,5-diaminopentane) is formed by the decarboxylation of lysine. This catabolism of lysine is characteristic of postmortem changes in animals. Therefore the estimation of cadaverine, as well as putrescine, levels in fish products is used for the estimation of food quality and safety (2,3,27). The ingestion of fish, which have been improperly handled or stored, is very often connected with so-called scombroid toxicity. The toxin is believed to consist of histamine, and possibly putrescine and cadaverine, which potentiate the toxicity of histamine. Putrescine and cadaverine inhibit the histamine-metabolizing enzymes, diamine oxidase and histamine N-methyl transferase (27). All physiological functions of cadaverine, if any, are yet unknown.

**Agmatine**

Agmatine (1-amino-4-guanidobutane) is an amine derived from the decarboxylation of L-arginine ([carboxy,1-amino]-4-guanidobutane) catalyzed by arginine decarboxylase (ADC). Agmatine is metabolized to putrescine by agmatinase. While prevalent in bacteria and plants, agmatine and its metabolic enzymes have only recently been identified in mammalian tissues. Agmatine has been proposed as the physiological ligand for the imidazoline receptors (6) and may be a novel neurotransmitter (20). It is not known whether agmatine is synthesized in the homeostasis of intracellular polyamine content, but its physiological significance is probably much more important than previously surmised just a few years ago.

Agmatine is a competitive NO synthase inhibitor but is not an NO precursor. In vitro $K_i$ values are approximately 660 mM for NO synthase (NOS-1), 220 mM for NO synthase-2, and 7.5 mM for NO synthase-3. Structurally related polyamines do not inhibit NOS activity. Agmatine, therefore, may be an endogenous regulator of NO production in mammals, although the requisite concentrations for inhibition of NOS-1 and NOS-2 are prohibitively high for effects requiring direct interactions. Reganathan et al. (19) observed that agmatine decreased the activity of NOS-2 by reducing the levels of enzyme protein as measured by immunoblot and immunocytochemistry. It was observed that a reduction in NO synthesis, as well as some other imidazoline agents inhibit the expression of NOS-2 and proliferation in primary glial cells and vascular smooth muscle cells (VSMC). Agmatine was also found in axons and axon terminals associated with small sympathetic vesicles in rat hippocampus (22). These findings further implicate agmatine as an endogenous neurotransmitter which may be co-released with L-glutamate and may act as a blocker of NOS and the NMDA receptor.

The distribution of agmatine was mapped in the CNS of the rat. Agmatine-containing neurons were present in the cerebral cortex, predominantly within laminae VI and V, and to a lesser extent, III, and mainly in retrosplenial, cingulate, primary somatosensory and auditory cortices, and the subiculum. In the lower brainstem, these neurons were selectively localized to visceral relay nuclei; the nucleus tractus solitarii and pontine parabrachial complex, and per...
and cultured cells, it was found that an early rise in the level of putrescine is important for hormonal and/or agonist stimulation of DNA synthesis (16). Putrescine binding to nuclear macromolecules has been proposed to modulate DNA synthesis and transcription. In many experimental cell systems, the polyamines sometimes act synergistically or antagonistically, making it difficult to distinguish their individual effects. Polyamines, spermine, spermidine, and putrescine, all exhibit antimutagenic potential against ethyl methane sulfonate (EMS)-induced mutations. In addition, spermidine and putrescine demonstrate potential to reduce the number of spontaneous revertants in modified Ames tests (17). The loss of feedback regulation of the polyamine transport system is sufficient to induce apoptosis (29).

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Putrescine

Putrescine (1,4-diaminobutane) is a product of conversion of agmatine by agmatinase or by decarboxylation of ornithine by ODC. In experiments with a variety of tissues and cultured cells, it was found that an early rise in the level of putrescine is important for hormonal and/or agonist stimulation of DNA synthesis (16). Putrescine binding to nuclear macromolecules has been proposed to modulate DNA synthesis and transcription. In many experimental cell systems, the polyamines sometimes act synergistically or antagonistically, making it difficult to distinguish their individual effects. Polyamines, spermine, spermidine, and putrescine, all exhibit antimutagenic potential against ethyl methane sulfonate (EMS)-induced mutations. In addition, spermidine and putrescine demonstrate potential to reduce the number of spontaneous revertants in modified Ames tests (17). The loss of feedback regulation of the polyamine transport system is sufficient to induce apoptosis (29).

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riventracular areas including the laterodorsal nucleus, locus coeruleus and dorsal raphe. In the midbrain, these cells were concentrated in the ventral tegmental area and periaqueductal gray. In the forebrain, subcortical-amine-containing neurons were obtained predominantly in the preoptic area, amygdala, septum, bed nucleus of the stria
terminals, midline thalamus, and the hypothalamus. Amine immunoreactivity was also affiliated with endo
plasmic reticulum and the plasmalemma (14). The central distribution of the antigen with the hypothesis that the amine may be a novel neurotransmitter of neurons involved in behavioral and visceral control.

Amine uptake into rat synaptosomes was investiga
ted by Saxte et al. (23). They found that transport was not inhibited by amino acids, polyamines, or monoamines, in
dicating that the uptake is not mediated by any primary amine-bearing compounds of these types. When they exa
mined the effects of some channel agents on amine uptake, Ca2+ ion was observed to increase it. In addition, some imidazole drugs, such as izidaxan and phenolami
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Amine in synaptosomes is present in brain and may be important in regu
lating the extracellular concentration of amine.

Plasma amine concentrations are very low in hu
mans. However, they are significantly elevated in depressed patients compared to controls. Treatment with an antidepressant bupropion normalized plasma amine lev
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Paradoxically, amine uptake is not directly on en
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view. As was observed by Schwartz et al. (26), amine also exerts stimulatory effects on glomerular ultrafiltration via a constitutive NOS-dependent mechanism and this does not require the participation of alpha 2-adrenergic receptors. It is thought that the pathogenic role of the bacterial pathogen, Helicobacter pylori, is able to form and release the endoge
nous imidazoline receptor ligand, agmatine, and that this may be a novel neurotransmitter in brain. Ann N Y Acad Sci 1999;881:332-43.

In gastric juice from H. pylori-positive patients than patients who are H. pylori-negative (10). The same unusual polyamines have been iden
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Unusual polyamines

Unusual polyamines are found in some plants and ther
mopharmacological vectors that the. Very often these unusual polya
mines occur simultaneously with the usual polyamines such as diaminopropionate, putrescine, cadaverine, spermidine, spermine, and agmatine. Aminopropoxyspermidine has been reported in the aquatic plants Brasenia schreberi and Nuphar japonicum belonging to the family Nymphae
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Tuapa natis belonging to the family Hydrocharitaceae γ-Guanidinooxypropylamine [H2N(NH=)CNHO(CH2)3NH2] , a new guanidino-
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Conclusions

Natural polyamines represent a group of compounds having major physiological significances. Since the bio
syntheses of the polyamines is tightly regulated and invol
ved in the control of many biological processes such as carcinogenesis, cell growth, cell differentiation, gene tran
scription and translation, their continued study is very im
portant for understanding critical processes in biological systems. Proponents of polyamine biosynthesis have potenti
al clinical uses as antioxidant and antiparasitic agents (28).

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Agmatine uptake into rat synaptosomes was investiga-
ted by Sastre et al. (23). They found that transport was not inhibited by amino acids, polyamines, or monoamines, in dicating that the uptake is not mediated by any primary amino-bearing compounds of these types. When they exa-
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take. Thus, a selective, Na+ ion-dependent uptake system for agmatine exists in brain and may be important in regu-
lating the extracellular concentration of agmatine.

Plasma agmatine concentrations are very low in hu-
mans. However, they are significantly elevated in depressed patients compared to controls. Treatment with the antidepressant bupropion normalized plasma agmatine le-
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ce from H. pylori-positive patients than patients who are H. pylori-negative (10).

Satriano et al. (24) proposed a novel regulatory pathway in which agmatine acts as an antiproliferative molecule and potential tumor suppressor by restricting the cellular poly-
amine supply required to support growth.

**Spermidine and spermine**

Spermidine (1,8-diamino-5-azacone) and spermine (1,12-diamino-5,9-diazadecane) are very ubiquitous tri-
and tetra-aminos, respectively, which frequently occur si-
multaneously in animal cells. Their physiological functions are generally similar. Their biosyntheses originate through initial aminopropylation of one primary amine group of putrescine to form spermidine. This is followed by a second aminopropylation addition to the primary amine group of spermidine, which initially derives from putrescine, to form spermine. Both reactions require decarboxylated S-
adenosylmethionine as the propylamine donor. Spermidine synthesis from putrescine is catalyzed by putrescine aminopropyltransferase (PAPT) and spermine synthesis from spermidine is catalyzed by spermidine aminopropyltransfe-
rase (SAPT). Spermidine and spermine are retroconverted to putrescine and spermine, respectively, by initial N-ac-
tylation and subsequent polyamine oxidation. The interme-
diate N-acetylputrescine, N-acetyl spermidine and N-
acetyl spermine are the major urinary N-acetylpolya-
mines. Polyamines and N-acetyl polyamines are terminally degradable to non-amino acid metabolites by oxidative dea-
imination and aldehyde dehydrogenation. Polyamine oxida-
tion, catalyzed by polyamine oxidase, has Recently been hypothesized to be a major contributor of cellular hydrogen peroxide, which commits many types of eukaryotic cells into an apoptotic pathway of cell death (3,15).

Spermine has been identified as a potent antioxidant and an anti-inflammatory agent. The compound is present in all animal cells and all organs. The concentration is extremely high in skin, and spermine constitutes a prime defense against radiation damage. This hypothesis is sub-
stantiated by the fact that ODC, the rate-limiting enzyme of spermine biosynthesis, is induced by UV irradiation and oxidative stress. Moreover, inhibition of ODC makes cells more sensitive to radiation damage. The antioxidative effect of spermine may be due to metal chelation and/or to pre-
vention of superoxide generation from stimulated neuro-
phil (8).

**Unusual polyamines**

Unusual polyamines are found in some plants and ther-
moregulatory microorganisms. They very often have unusual poly-
amines occur simultaneously with the usual polyamines such as diaminopropionate, putrescine, cadaverine, spermidine, spermine, and agmatine. Aminopropophosphospermidine has been reported in the aquatic plants *Brassica* *schreberi* and *Nuphar japonicum* belonging to the family Nymphae-
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tified in water-deficient stressed *Medicago sativa* L. (alfalfa) and the photosynthetic acidobacteriophaga. *Cauli-mus caldarium*. Thermotolerance was detected in *Brassica* *schreberi* and *Nuphar japonicum* more recently in *Medicago sativa* L. *N-(Bow-3)-N,N,N,N-12-ethanediamine* [H(N(CH2)4)NH(N(CH2)4)NH2], was discovered in the aquatic plant *Nuphar japonicum*. N-Methylspermidine [H(N(CH2)4)N(CH2)4N(CH2)4NH2] was discovered in the water chestnut *Trapa natans* belonging to the family Hydrocharaceae. γ-Guanidinoxypropylamine [H(N(NH)2)N(CH2)4NH2], a new guanidino polyamine, has been isolated from *Trapa* fruitseeds and seedlings of the sword bean, *Canavalia gladiata* (5).

Many unusual polyamines have been identified in extre-
me thermophiles (13), such as thermine (norspermine),
camaldehyde, caldohexamine, tris-J-amino-
propylamine, thermospermine, caldine (norses-
pirnidine), and tetrais(J-amino)propylamine, ammonium and others. Chemical structures for some unusual polyamines are given in Fig. 3.

**Conclusions**

Natural polyamines represent a group of compounds having major physiological significances. Since the bio-
syntheses of the polyamines is tightly regulated and invol-
ved in the control of many biological processes such as carcinogenesis, cell growth, cell differentiation, gene tran-
scription and translation, their continued study is very im-
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amine supply required to support growth.

*Fig. 3: Chemical structures of some uncommon (unusual) polyamines.*

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Mitoxantrone dihydrochloride, a synthetic anthraquinone, is a potent antineoplastic agent and active substance of REFADOR Inj. PLIVA-LACHEMA. The chemical structure and chemical name are:

\[
\begin{align*}
\text{OH} & \quad \text{O} & \quad \text{H} & \quad \text{N} & \quad \text{NH} & \quad \text{OH} \\
\text{OH} & \quad \text{O} & \quad \text{H} & \quad \text{N} & \quad \text{NH} & \quad 2 \text{HCl}
\end{align*}
\]

1,4-dihydroxy-5,8-bis\{2-(2-hydroxyethyl)amino\}anthracene-9,10-dione dihydrochloride.

This active component of the preparation is manufactured by the Research Institute of Organic Synthesis (VÚOS) (17) Pardubice, Czech Republic.

Mitoxantrone (MX) can be used alone and in combination with other agents against various types of neoplasias, including solid tumours (8) and haematological malignancies (14,20). Among substances used to give metabolic support, we tried pre-clinically to determine whether some L-carnitine derivatives, in combination with MX could ameliorate the host’s metabolic response to tumour processes. The aim was to document new possibilities of using a combination of chemotherapeutics with substances that modulate their therapeutic and toxicologic profiles and that could be of clinical importance as new antitumour drugs and new therapeutic protocols.

In this work we investigated the therapeutic benefit of acetyl-L-carnitine (ALC) in combination with MX on a murine leukemia L1210 resistant to MX. The effect of ALC in combination with MX on DBA/2 male mice bearing a transplantable L1210 leukemia resistant to MX was proven at a level of probability \( p \leq 0.001 \). The effect of ALC in monotherapy was not demonstrable.

**Key words:** Mitoxantrone dihydrochloride (MX); Acetyl-L-carnitine hydrochloride (ALC); Protective effect and L1210 leukemia

**Introduction**

Mitoxantrone dihydrochloride, a synthetic anthraquinone, is a potent antineoplastic agent and active substance of REFADOR Inj. PLIVA-LACHEMA. The chemical structure and chemical name are:

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\begin{align*}
\text{OH} & \quad \text{O} & \quad \text{H} & \quad \text{N} & \quad \text{NH} & \quad \text{OH} \\
\text{OH} & \quad \text{O} & \quad \text{H} & \quad \text{N} & \quad \text{NH} & \quad 2 \text{HCl}
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1,4-dihydroxy-5,8-bis\{2-(2-hydroxyethyl)amino\}anthracene-9,10-dione dihydrochloride.

This active component of the preparation is manufactured by the Research Institute of Organic Synthesis (VÚOS) (17) Pardubice, Czech Republic.

**Materials and methods**

Mitoxantrone (batch No 12/309 VÚOS) was purchased from the Research Institute of Pharmacy and Biochemistry.

**Summary:** Supportive care in tumour chemotherapy is a subject of intensive research. The complications of cytostatic therapy are a cause of extensive research of their pharmacological interactions and side effects. The immunologic and biochemical changes accompanying tumours are the factor that is most responsible for the worsening of the physiology of the host. Regimens containing carnitine and its acetyl derivative are used in many cases, among others even for preventing hepatotoxicity. Our hypothesis was to verify the supporting metabolic effects of acetyl-L-carnitine hydrochloride (ALC) in combination with mitoxantrone (MX) and hepatotoxic cytostatic drugs including alkylating agents. This present report describes the effect of ALC in combination with MX on DBA/2 male mice bearing a transplantable L1210 leukemia resistant to MX. The criterion for evaluation of effect was the length of survival time of experimental animals. The proportional-hazard model quadratic in the drug dose (7) was used for survival time evaluation and optimal dose calculation. The hazard functions and the indexes of relative hazard were determined using Weibull distribution after logarithmic transformation of the entered data in each particular group. The dose-response curve was represented by a second-degree polynomial without absolute term. The combination therapy revealed that the optimal dose of ALC was 186 mg/kg s.c. This relation is shown in Fig.1. A significant effect of ALC (s.c.) in combined therapy with MX (6 mg/kg i.v.) given to animals bearing an experimental form of leukemia L1210/MX resistant to MX was proven at a level of probability \( p \geq 0.001 \).

The effect of ALC in monotherapy was not demonstrable.

**Key words:** Mitoxantrone dihydrochloride (MX); Acetyl-L-carnitine hydrochloride (ALC); Protective effect and L1210 leukemia