# 15. ANTIMICROBIAL AND ANTITUMOR EFFECTS OF ERGOT ALKALOIDS AND THEIR DERIVATIVES

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## 15.1. INTRODUCTION

Ergot alkaloids and their derivatives are able to inhibit the growth of certain hormone-dependent tumors *via* the inhibition of prolactin release from the anterior pituitary gland (Cassady and Floss, 1977). The therapy of the prolactinoma, an adenoma of this gland, and other prolactin-producing tumors by e.g. bromokryptine or lisuride is of clinical relevance (Thorner *et al.*, 1980). The inhibition of prolactin release is mediated by stimulation of dopamine $D_2$-like receptors. However, there is a completely different mode of action which is responsible for antitumor properties of certain ergolines. The latter was detected in connection with the discovery of the antimicrobial activity of clavine-type ergot alkaloids.

## 15.2. ANTIMICROBIAL EFFECTS

Investigations on the transformation of different ergot alkaloids by microorganisms in the early eighties led to the observation that the addition of agroclavine to cultures of *Streptomyces purpurascens* caused a pronounced growth inhibiting effect (Schwarz, 1978; Schwarz and Eich, 1983). The biogenetically closely related elymoclavine was less active whereas the lysergic acid amides ergometrine and ergotamine showed almost no influence on the growth of the bacteria. It was demonstrated that no essential metabolization of these clavines took place during incubation so that there was no doubt about the direct antibiotic activity of the two clavines (Schwarz and Eich, 1983; Eichberg, 1983). The effect of agroclavine could be increased by hydrogenation at the 8, 9 position to give festuclavine, another natural compound (Eich and Eichberg, 1982; Eichberg, 1983). Certain 1-alkyl and 6-alkyl-6-*nor* derivatives of festuclavine showed a further enhancement of this effect. This turned out to be also true for human pathogenic bacteria species. For example, 6-allyl-6-*nor*-festuclavine exhibited an inhibitory activity against e.g. *Staphylococcus aureus* (MIC: 30

µg/ml) and 1-propyl-6-*nor*-festuclavine was active against e.g. *Escherichia coli* (MIC: 60 µg/ml). On the other hand, the natural compounds agroclavine and festuclavine showed only moderate inhibitory effects (MIC: 200 µg/ml) (Eich *et al.,* 1985a). More or less strong bacteriotoxic activity was also found for a series of clavine derivatives in mutagenicity studies with different strains of *Salmonella typhimurium* and one strain of *Escherichia coli* (Glatt *et al.,* 1987, 1992).

In contrast to the remarkable effects of certain clavine derivatives on the growth of bacteria, no comparable influence on fungi could be observed. Yeasts like *Saccharomyces uvarum* or the pathogenic *Candida albicans* as well as the mold *Blakeslea trispora* were not inhibited by agroclavine or its derivatives. Only a modest effect was shown for certain derivatives of festuclavine in experiments with *C. albicans* (MIC: 250–500 µg/ml) (Schwarz and Eich, 1984; Eich *et al.,* 1985a).

## 15.3. CYTOSTATIC EFFECTS OF AGROCLAVINE AND FESTUCLAVINE

Using a L5178y mouse lymphoma cell system it was shown that agroclavine and festuclavine are potent cytostatic agents *in vitro* (Eich *et al.,* 1984a, b, c, 1986b). Their $EC_{50}$ values of 6.3µM and 7.1 µM, respectively, were comparable in potency with the $EC_{50}$ value of the therapeutically used cytostatic alkaloid camptothecin (7.2 µM). Surprisingly, other natural 6, 8-dimethylergolenes structurally related to agroclavine (lysergine, isolysergine, setoclavine, isosetoclavine) and other natural 6, 8-dimethylergolines structurally related to festuclavine (pyroclavine, costaclavine) were inactive (Faatz *et al.,* 1989, 1990; Faatz, 1991). Though elymoclavine had shown some bacteriotoxicity neither this alkaloid nor other natural 8-hydroxymethyl-6-methylergolenes (lysergol, isolysergol, penniclavine) including the 8-hydroxymethyl-6-methylergoline dihydrolysergol-I showed cytostatic activity (Eich *et al.,* 1986a). This was also true for the two unusual clavines lysergene and chanoclavine-I as well as for lysergic acid derivatives like methylergometrine, lysergic acid amide, lysergic acid diethylamide (LSD), and isolysergic acid amide (Eich *et al.,* 1984a, 1997).

Thus, agroclavine and festuclavine possess unique biological activities as members of the ergot alkaloid family. This might be not only important for potential drugs of the future but also of relevance concerning aspects of chemical ecology (Eich, 1992). Since agroclavine, a precursor in the biosynthesis of lysergic acid derivatives in *Claviceps purpurea,* is the main alkaloid in the early stage of the sclerotia development, it may be useful as a protecting antimicrobial and cytostatic agent in this colourless, soft and wet mycelium phase.

## 15.4. AGROCLAVINE AND FESTUCLAVINE AS LEADS FOR THE DEVELOPMENT OF ANTITUMOR DRUGS

Agroclavine and festuclavine showed like other ergot alkaloids interactions with α-adrenoceptors, 5-HT receptors, and DA receptors as agonists, antagonists, or partial agonists, respectively (Fuxe *et al.,* 1978; Pertz, 1996). Moreover, festuclavine exhibited direct mutagenicity in the Ames test as well as agroclavine in the presence of a liver xenobiotic metabolizing system (Glatt *et al.,* 1992).

For the development of clavines as potential antitumor agents four main aims were of particular importance: (1) Variations of the ergoline nucleus and structure-activity relationship studies in order to find compounds with increased cytostatic potency *in vitro*. (2) Development of active compounds with enhanced metabolic stability since ergolines usually are metabolized very quickly *in vivo* (pronounced first pass effect). (3) Dissociation between antineoplastic and mutagenic activities presumed the latter is not the mechanism of action for the first. (4) Decrease of their affinity for neurotransmitter receptors mentioned above on the assumption that the

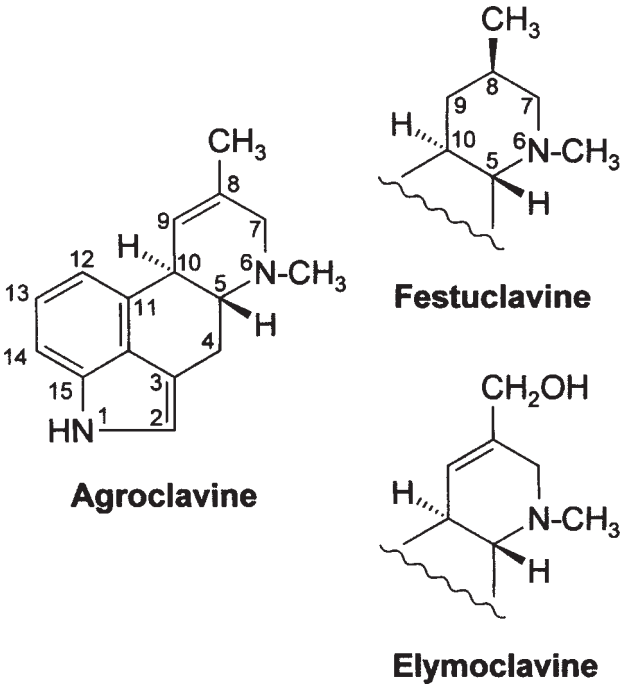


**Figure 1** Naturally occurring clavines as leads for antimicrobial and cytostatic agents

cytostatic effect is not based on the interaction with any of these receptors. Otherwise cytostatic clavines could not be suitable for the therapy of cancer diseases because of severe adverse effects.

## 15.5. INFLUENCE OF DIFFERENT SUBSTITUTIONS ON THE CYTOSTATIC ACTIVITY OF CLAVINES *IN VITRO*

*Substitution at N-1:* 1-Alkylation (Eich *et al.,* 1985b) significantly enhanced the cystostatic effect of agroclavine and festuclavine, respectively. Those homologues which bear a three to six carbon atoms membered straight-chain substituent at N-l were especially effective with $EC_{50}$ values between 0.87μM (1-pentylagroclavine) and 1.6 μM (1-hexylagroclavine) (Eich *et al.,* 1986b). The cytostatic potential of these clavine derivatives is rather high compared with clinically used cytostatic antibiotics which reduce cell proliferation under identical *in vitro* conditions at similar concentrations ($EC_{50}$ of 1.0 μM for bleomycin; $EC_{50}$ of 1.2 μM for doxorubicin; $EC_{50}$ of 1.9 μM for daunorubicin). 1-Pentylagroclavine was active in 27 different human and non-human cancer cell systems of the National Cancer Institute, Bethesda/MD (USA) with $IC_{50}$values between 2.0 and 8.0 μM (Faatz *et al.,* 1989, 1990).

Surprisingly, 1-alkylation of elymoclavine caused potent inhibition of the cell proliferation at an order of magnitude similar to that of the agroclavine series in spite of the fact that the parent compound elymoclavine was inactive by itself (Eich *et al.,* 1986a). Moreover, the acute toxicity (mouse, i.p.) was diminished considerably by 1-alkylation of the clavines (Eich *et al.,* 1984b).

Since the n-alkyl substituent is metabolically not very stable, the cycloalkyl and cycloalkylmethyl groups which are known to be more stable should be of advantage. Such derivatives were also very active *in vitro,* e.g. 1-cyclohexylfestuclavine ($EC_{50}$: 2.1μM) and its 1-cyclohexylmethyl analogue ($EC_{50}$: 1.7 μM) (Kasper *et al.,* 1989; Kasper, 1991). Again corresponding substitutions of the inactive pyroclavine afforded compounds of high potency indicating the importance of the lipophilic substituent at N-1 (Faatz *et al.,* 1989; Faatz, 1991).

Substitution at N-1 by *ß*-ribofuranosyl or *ß*-2-deoxyribofuranosyl residue should create compounds analogous to nucleotides where more profound cytostatic and/or antiviral effect can be expected. Series of *ß*-ribosides (Křen *et al.,* 1997a, b) and *ß*-deoxyribosides (Křen *et al.,* 1997c) were prepared from clavine alkaloids (agroclavine, elymoclavine, lysergol, lysergene). The compounds were tested against a large set of viruses including HIV. All compounds tested displayed higher cytotoxicity towards the host cells and, therefore, their use as antivirals is excluded. The compounds are now being tested for antineoplastic activity and especially agroclavine ribosides show promising results.

*Substitution at C-2:* In order to avoid metabolic attack at the 2,3 double bond, suitable substituents at C-2 should be useful since other ergolines like lisuride show metabolic profiles which include oxidations at these positions (Hümpel *et al.,* 1984). However, different substitutions of festuclavine (e.g. -Cl, -Br, -I, -$CH_2OH$, -CHO, -$SCH_3$, -$SC_2H_5$) led to compounds with diminished activity or even to its total loss (Faatz, 1991; Milhahn, 1997). But there were some exceptions, e.g. 2-(2-nitro-phenyl)thiofestuclavine ($EC_{50}$: 4.4 µM) and 2-ethinylagroclavine ($EC_{50}$: 3.0 µM) (Eich *et al.,* 1997).

*Substitution at N-6:* Removal of the methyl group at N-6 resulted in a marked loss of activity for agroclavine and festuclavine (Eich *et al.,* 1986b, c). Re-alkylation at N-6 with $C_2$- to $C_7$-membered straight-chain substituents led to compounds with similar potency as agroclavine itself. Interestingly, 1-alkylation of 6-*nor*agroclavine or 6-*nor*festuclavine revealed compounds with a potency which was almost equivalent to the 6-methylated analogues. The ring D opened 6-methyl-6,7-secoagroclavine was inactive (Eich *et al.,* 1997).

*Substitution at C-7:* The 7-oxo derivative of the inactive alkaloid lysergene was a potent cytostatic agent (Pertz *et al.,* 1989).

*Substitution at C-10:* Alkylation at C-10 seems to have a similar consequence for the extent of the cytostatic activity as alkylation at N-l, e.g. the $EC_{50}$ values of 10α-pentylagroclavine versus 1-pentylagroclavine were l,3 µM: 0,9 µM (Faatz *et al.,* 1990; Faatz, 1991).

*Substitution at C-13:* Bromination at C-13 should avoid the metabolic hydroxylation at this position as well as at the vicinal C-12 position. Thus, it was of advantage that 13-bromo-festuclavine was twice as active *in vitro* as festuclavine itself. Once more 1-alkyl and 1-cycloalkyl derivatives were even more active (Eich *et al.,* 1987; Pertz *et al.,* 1987).

## 15.6. MECHANISM OF ACTION

In a first approach to determine the mode of action of the cytostatically active clavines, incorporation studies were performed (Eich *et al.,* 1984a). They revealed that the incorporation of [$^3$H]-thymidine into DNA is reduced in the presence of 1-propylfestuclavine. On the other hand, no influence has been determined for [$^3$H]-uridine incorporation into RNA and [$^3$H]-phenylalanine incorporation into protein. The inhibition of the thymidine incorporation rate was only observed after a preincubation period with the clavine derivative for 24 h and was not detectable after a pretreatment period of 2h. The assumption was favoured that clavines interfere with DNA replication processes in L5178y cells rather than an unspecific effect on cell growth. This conclusion was based on the observation that all active clavines caused "unbalanced growth", a property which they share with other cytostatic agents acting selectively by

inhibition of DNA synthesis. Experiments with 1-propylelymoclavine revealed that at low concentrations again only the thymidine incorporation rate was significantly reduced. At higher concentrations of the cytostatic agent an additional decrease in the incorporation rates of uridine and phenylalanine was observed (Eich *et al.,* 1986a). From these results, it was concluded that 1-propylelymoclavine also inhibits primarily DNA synthesis by an unknown mechanism. The influence of 1-propylagroclavine on the synthesis of the macromolecules in L5178y cells was comparable to the corresponding festuclavine and elymoclavine analogues. Interestingly, the reduction of cell growth by 50% occurred at a concentration which was very close to that causing a 50% reduction of DNA synthesis. It has been clarified that this inhibition was not due to a direct effect on DNA polymerase α or *ß*. Therefore, an interference with the state of organization of the nuclear reticulum was postulated (Eich *et al.,* 1986b).

The nucleoside uptake and incorporation into DNA and RNA in human lymphoid leukemia Molt 4B cells was also dose-dependently inhibited by higher concentrations of several growth depressing festuclavine derivatives (Hibasami *et al.,* 1990). The most powerful growth inhibiting derivative, 13-bromo-l-cyclopropylmethylfestuclavine, showed complete suppression of nucleoside uptake and incorporation into the macromolecules at a concentration of 50μM. These results were in favour of the suggestion that the inhibitory effects on nucleoside incorporation into DNA or RNA were merely due to inhibition of cellular uptake of nucleosides.

An obvious mechanism of action could involve the interaction with a neurotransmitter receptor since clavines interact with DA receptors, 5-HT receptors, and α-adronoceptors, respectively. But this is apparently not the case (Eich *et al.,* 1986b). The mechanism of action seems to be a fundamentally new one for ergoline compounds.

Agroclavine as well as its 1-propyl- and 1-pentyl derivative, respectively, are not directly mutagenic in the AMES test with different strains of *Salmonella typhimurium* and one strain of *Escherichia coli* (Glatt *et al.,* 1987). Addition of a subcellular rat liver preparation forming a xenobiotic metabolizing system (S9) resulted in a substantial decrease of cytotoxicity and in the formation of mutagens. The nature of the mutagenic metabolites is unknown. The agroclavine skeleton offers a number of possible sites for oxidative transformations by liver preparations. It is unlikely that a genotoxic mechanism is involved in the antineoplastic activity of the clavines since L5178y lymphoma cells in culture express extremely low levels of cytochrome P450, which are the major active enzymes contained in the liver S9 preparation. This notion is supported by the lack of a correlation between the mutagenic activities in *S. typhimurium* and the cytostatic activities in L5178y cells of a series of clavine derivatives. In addition, there was no correlation between the cytostatic activities of these compounds in L5178y cells and their bacteriotoxic activities in *S. typhimurium* (Glatt *et al.,* 1992). It is not clear

therefore whether cytostatic and bacteriotoxic activities are due to independent mechanisms or are mediated by orthologous receptors differing in their affinity spectrum for ligands. The dissociation between cytostatic, bacteriotoxic and mutagenic activities suggests that it may be possible to develop derivatives that are cytostatic but not mutagenic and antimicrobial.

## 15.7. ONCOSTATIC ACTIVITY *IN VIVO*

For the development of clavines as potential antitumor agents four main aims were postulated above. The development from agroclavine and its highly active 1-pentyl derivative, both inactive *in vivo,* led via numerous derivatives to 13-bromo-l-cyclopropylmethylfestuclavine and the corresponding 13-bromo1-cyclopentyl derivative which showed pronounced antineoplastic activity *in vivo* (Eich *et al.,* 1987; Pertz, *et al.,* 1987; Faatz *et al.,* 1989; Hibasami *et al.,* 1990; Kasper, 1991; Glatt *et al.,* 1992). Treatment with 13-bromo-l-cyclopropylmethylfestuclavine increased the median life span (survival time) of mice (lymphoma L5178y; 50mg/kg) more than 2-fold (T/C: 212%; mean dead rate: 35.2 days versus 16.6 days). The T/C value of the 1-cyclopentyl analogue was 223%. However, these compounds showed mutagenicity as well as (an undesired) mitigated cytotoxicity in the Ames test in the presence of the hepatic xenobiotic metabolizing S9 system (Glatt *et al.,* 1992). It was assumed that this could be due to the metabolic formation of certain oxygen species at C-2/C-3 (Milhahn *et al.,* 1993). The 2-methylthio derivative of 13-bromo-l-cyclopropylmethylfestuclavine which should prevent such a metabolization turned out to possess an equivalent cytostatic activity *in vitro* (Milhahn, 1997). Further studies will show if this is also the case *in vivo*. Moreover, an additional metabolic stabilization at N-6 could be of advantage. Such compounds should be promising candidates for *in vivo* experiments.

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