Chapter 14: Ergot alkaloids

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14.1 History of Ergot Alkaloids

Ergot alkaloids are produced in sclerotia of grass symbionts, namely fungi of the genus *Claviceps*, along with other filamentous fungi in the genus *Aspergillus, Neotyphodium, Arthroderma, Penicillium, Epichloe, Balansa* and the recently described *Periglandula*. The EA have been referenced in ancient history. Abnormally infected grain was noticed as early as 1900–1700 BC, in Mesopotamia, and by 600 BC the Assyrians were able to differentiate between different diseases affecting grain. References to grain diseases have also been found in the Bible, in the Old Testament (850–550 BC). Ergots were used in 1100 BC in China for the treatment of various obstetric conditions. The Eleusinian Mysteries of ancient Greece were linked to hallucinations caused by EA. In 550 BC, the Egyptians recommended a mixture of ergot, oil and honey as a treatment for hair growth. Moreover, in about 350 BC, the Parsi wrote about the “noxious grasses that cause pregnant women to drop the womb and die in childbirth”.

In the Middle Ages, the first reported ergotism epidemic was in 944–1000 AD, when about half the population of the Aquitane region of France (about 60,000 people) died of ergot poisoning. Other epidemics have occurred in Germany in 1581, 1587 and 1596, largely due to consumption of contaminated rye flour. In 1764, Von Munchhausen finally recognized the causative agent of ergotism as a fungus that parasitizes grain crops. The
gangrenous form of the disease (*Ergotismus gangraenosus*) was commonly known as “ergotism”, “holy fire”, “infernal fire” or “St. Anthony’s fire”. Symptoms include delirium and hallucinations, muscle spasms, convulsions and gangrene of the limbs. Livestock is also subject to similar symptoms upon poisoning by EA. Ergotism was associated with the Salem Witch Trials and the Great Fear of the French Revolution. At the end of the 17th century, people finally associated ergotism with the consumption of infected rye and general awareness and knowledge reduced these mass poisonings. The early medicinal uses of ergots were documented first in 1582, for a “quickening child-birth”. However, after the number of stillborn neonates increased, the Medical Society of New York initiated an investigation, which resulted in a reduction of the use of ergots only to control postpartum haemorrhage. The history of medicinal applications of ergot alkaloids is very rich, due to their high biological activity (see Section 14.7) and, undoubtedly, further applications remain to be discovered.

### 14.2 Ergot Alkaloid Classes

All naturally occurring ergot alkaloids share a common tetracyclic scaffold, the so-called “ergoline scaffold” (Figure 14.1A). EA are divided into three major classes based on the substituents that decorate this scaffold: clavines (festuclavine and agroclavine derived), simple lysergic acid derivatives and ergopeptides. The clavines include partially or fully saturated ring species D such as agroclavine 1 or festuclavine 2 (Figure 14.1B). Simple lysergic acid derivatives consist of the basic D-lysergic acid structure as an alkyl amide (Figure 14.1C) and ergopeptides based also on D-lysergic acid and a cyclic tripeptide moiety (Figure 14.1D).

### 14.3 Production of Ergot Alkaloids in Nature

Ergot alkaloids are produced by fungi belonging to the family *Clavicipitaceae; Claviceps purpurea* and *Neotyphodium lolii* from the order *Eurotiales*, which are parasitic or mutualistic plant symbionts, are well-known examples. Another known EA producer, *Aspergillus fumigatus* from the order *Eurotiales*, is an opportunistic pathogen of mammals. Notably, this diverse group of fungi produces surprisingly similar alkaloid profiles. Derivatives of lysergic acid and ergopeptides (Figure 14.1, C, D) are produced by *Clavicipitaceous* fungi *Claviceps purpurea* and *Neotyphodium lolii*, and are believed to protect the fungi from predation by mammals and insects. Clavine-type ergot alkaloids (Figure 14.1B) are produced by *Aspergillus fumigatus* and *Aspergillus japonicus* during conidiation. However, the biological role of EA in the survival of conidia during invasive aspergillosis is not completely understood. Recently, the *Arthrodermataceae* family of fungi has been studied in the context of EA production. It was demonstrated that *Arthroderma benhamiae* produces chanoclavine-I aldehyde 14 (Figure 14.2), the common biosynthetic intermediate of all EA biosynthesis. Finally,
**Figure 14.1**  
A. Tetracyclic ergoline ring structure with conventional numbering and lettering.  
B. Examples of clavines.  
C. Simple lysergic acid derivatives.  
D. Ergopeptides consist of D-lysergic acid with a cyclic tripeptide moiety.
Pleurobranchus forskalii, a species of marine gastropod mollusc is responsible for production of an ergot alkaloid peptide ergosinine, indicating that ergots may also be produced in marine organisms.\textsuperscript{14}

Ergot alkaloids have also been found in plant taxa Convolvulaceae (Solanales), which is known to be associated with Clavicipitaceae fungi.\textsuperscript{15,16} Recently, one of the unresolved questions why these alkaloids are present in such diverse taxa as the fungal Clavicipitaceae and a higher plant family as Convolvulaceae, has been answered. While horizontal gene transfer or a
repeated origin of the EA biosynthetic pathway has been proposed, recent work has shown that the morning glory family (Convolvulaceae) is colonized by an ergot alkaloid-producing Clavicipitaceous fungus and is seed-transmitted. It has been demonstrated that treatment of the colonized host leaves with fungicides led to elimination of leaf-associated fungus and concomitant loss of alkaloids from the plant. It turned out that these endophytic fungi live in a mutualistic symbiosis with plants and cause no symptoms of infection. The defensive mutualism relies on production of these alkaloids by plants for a protection from herbivores. In turn, fungi benefit from being in a protected position and receiving nutrition from the plant. Therefore, the ecological role of ergot alkaloids is to support environmental tolerance of plants, their fitness, resistance from drought and feeding deterrence from mammals and insects. It has been proven that the fungal symbionts are vertically transmitted through the seed of the narrow range of the host plant. However, the mechanism of how the fungi spread in the host plant remains cryptic. There are no signs of penetration of the plant epidermis by an epibiotic fungus. It has been observed that fungal hyphae are in close contact with the oil secretory glands of the plant cuticle, which may play a major role in the metabolic interaction fungus–host plants.

### 14.4 Biosynthesis of Ergot Alkaloids

#### 14.4.1 Biosynthetic Pathway

The EA biosynthetic pathway was initially investigated through feeding of isotopically labelled substrates to cultures of *C. purpurea*, which led to a proposed biosynthetic pathway for these alkaloids (Figure 14.2). In the first step of EA biosynthesis L-tryptophan is prenylated by dimethylallyl pyrophosphate (DMAPP), to yield 4-(γ, γ-dimethylallyl)tryptophan (DMAT). In the next step DMAT is N-methylated to yield 4-dimethyl-L-abrine (N-Me-DMAT). N-Me-DMAT is in turn converted into chanoclavine-I through series of successive oxidation steps that catalyze the intramolecular cyclization of the prenyl and indole moieties to form ring C. Subsequently, chanoclavine-I is oxidized to form chanoclavine-I-aldehyde, which is the last common precursor of all classes of ergot alkaloids. At this crucial branch point, chanoclavine-I-aldehyde can undergo intramolecular cyclization to form either fully saturated ring D of tetracyclic festuclavine or the unsaturated ring D of agroclavine. Festuclavine 2 and agroclavine then branch into lysergic acid amides/peptides and fumigaclavine type EA, respectively, as described in Section 14.4.4 (Figure 14.2).

#### 14.4.2 Gene Clusters

Ergot alkaloid biosynthetic genes have been demonstrated to be clustered on the genome of *A. fumigatus* (Figure 14.3A) and *Clavicipitaceae* fungi.
C. purpurea\textsuperscript{37,38} (Figure 14.3B), C. fusiformis\textsuperscript{39} (Figure 14.3C), N. lolii\textsuperscript{40} (Figure 14.3D), Arthroderma benhamiae\textsuperscript{13} (Figure 14.3E) and Epichloë sp.\textsuperscript{41} Homologues common among these species participate in the early steps of ergot biosynthesis. Species-unique genes are most likely responsible for further downstream modifications that result in the production of specific ergot alkaloid classes unique to each individual species, as discussed further in Section 14.4.4 (Figure 14.3). Tsai \textit{et al.} have successfully identified and cloned the gene coding for \textit{L-tryptophan dimethylallyl prenyl transferase} (DmA\textit{W}) from \textit{C. purpurea}.\textsuperscript{42} This discovery allowed the identification of the ergotamine biosynthesis cluster (68.5 kb) from \textit{C. purpurea} – the first ergot gene cluster to be discovered – \textit{via} chromosome walking (Figure 14.3).\textsuperscript{37} This gene cluster included open reading frames encoding non-ribosomal peptide synthetase (NRPS) modules (Lps1 and Lps2) that would be expected to be involved with the later biosynthetic pathway formation of ergopeptides.\textsuperscript{43–45} Moreover, it was observed that comparison of cluster sequences within \textit{C. purpurea} strain P1 (ergotamine producer) with strain \textit{C. purpurea} ECC93 (ergocristine producer) displayed conservation of most genes associated with formation of the ergoline ring, yet displayed high variation in genes associated with the NRPS production of the peptide ergot moiety.

A recent review by Schardl \textit{et al.} compares ergot alkaloid profiles, biosynthetic genes and genomic arrangements of those genes among 15 Clavicipitaceae.\textsuperscript{2,46} The dramatic differences in ergot alkaloid profiles are caused by the presence of specific mid-pathway or late-pathway genes, as well as differences in substrate or product specificity due to gene sequence variations. The authors correlated chemotypes of \textit{Claviceps} species with the presence or absence of the genes \textit{lpsA, lpsB, lpsC, easH, easO and easP}. This comprehensive work exhibits association of particular fungi with particular metabolites, which in turn reveals evolutionary changes in this pathway. A gene cluster for EA biosynthesis that was subsequently found in \textit{Neotyphodium} sp. \textit{Lp1} (a natural hybrid \textit{Neotyphodium lolii×Epichloë typhina}), studied by Panaccione \textit{et al.},\textsuperscript{47} allowed the experimental validation that disruption of the NRPS Lps1 homologue (\textit{LpsA}) involved in ergopeptide biosynthesis causes the loss of downstream alkaloid ergovaline. Fleetwood \textit{et al.} later identified part of the ergot alkaloid cluster for ergovaline biosynthesis (~19 kb) in \textit{N. lolii} using both chromosome walking and southern blot (Figure 14.3D).\textsuperscript{40} It was unambiguously demonstrated that the LpsB gene in \textit{N. lolii}, a homologue of the \textit{C. purpurea} Lps2, was associated with ergovaline production.\textsuperscript{40}

The discovery of \textit{A. fumigatus} biosynthetic gene cluster (22 kb) was facilitated by the published genome sequence of \textit{A. fumigatus}, which was associated with the production of fumigaclavines A, B, C, (21, 20, 17, respectively) and festuclavine 2.\textsuperscript{9} Further analysis of gene function in this cluster led to the characterization of easF and easD gene products, which are responsible for catalysing early steps in the ergot pathway.\textsuperscript{48,49} A recent survey of various isolates of \textit{A. fumigatus} were shown to have variable production of ergot alkaloids, which could be linked to changes in the ergot gene cluster.\textsuperscript{50}
Genome sequence analysis of fungi of the *Arthrodermataceae* revealed the presence of a gene cluster with high sequence similarity to those involved in the early common steps of ergot alkaloid biosynthesis in *Aspergillus fumigatus* and *Claviceps purpurea*. However, this system has not been studied in depth.

### 14.4.3 Early Ergot Alkaloid Biosynthetic Enzymes

The enzymology of EA biosynthesis is fascinating, and a number of gene products from these ergot alkaloid biosynthetic clusters have been biochemically characterized *in vitro*. The first step of the EA biosynthetic pathway is catalyzed by dimethylallyl prenyltransferase (DmaW) from cultures of ergot alkaloid producing *C. fusiformis*. DmaW prenylates L-tryptophan via an electrophilic aromatic substitution reaction. Recent work suggests the mechanism involves substitution on C-3 (instead of substitution on weakly nucleophilic C-4, as previously suggested) followed by a Cope rearrangement (Figure 14.2). Furthermore, two lysine amino acids have been implicated in the mechanism. DmaW homologues from *A. fumigatus*, *C. purpurea* and *N. lolii* have also been characterized. The structure of this enzyme has been solved recently, which facilitates an understanding of this enzyme’s specificity for the substrate and regioselectivity. Recently, it was demonstrated that alternate substrates, 4-methyltryptophan, 4-methoxytryptophan and 4-aminotryptophan, can also be prenylated by DmaW.

The next enzyme in the early pathway, EasF belongs to the N-methyltransferases enzyme family and is responsible for N-methylation of DMAT. EasF was first purified by Otsuka *et al.* from cell free cultures of *C. purpurea*. This enzyme methylates the amine nitrogen of dimethylallyl tryptophan using the S-adenosyl methionine (SAM) co-factor. After the identification of the ergot biosynthetic gene cluster in *A. fumigatus*, the easF gene was successfully cloned and heterologously expressed. The expressed EasF could also methylate DMAT to yield N-Me-DMAT (dimethylallyl L-abrine). Following methylation by EasF, two oxidation reactions are proposed to transform N-Me-DMAT to chanoclavine-I, thus forming ergoline ring C. Kozikowski *et al.* predicted these two oxidation steps of the pathway based on isotopic feeding studies. They observed that a proposed diene intermediate was incorporated into downstream ergot alkaloids upon feeding to *C. purpurea* and that oxygen from hydroxyl group of chanoclavine-I was incorporated from molecular oxygen. Enzyme candidates for carrying out oxidation reactions were proposed to be EasC and EasE. These enzymes display protein sequence similarity to catalases and FAD oxygenases, respectively. The role of the EasE and EasC in the oxidations of N-Me-DMAT to chanoclavine-I in *C. purpurea* has also been demonstrated by gene disruption experiments. The disruption of easE and easC genes in *A. fumigatus* indicate that EasC and EasE are both required for ring C formation. Heterologous expression of EasC revealed a
catalase activity of this protein. However, demonstration of in vitro activity for EasE has remained elusive.

EasD is an NAD⁺ binding oxidase that is responsible for the oxidation of the hydroxyl group of chanoclavine-I to carbonyl group of chanoclavine-I-aldehyde. EasD was initially cloned and characterized from *A. fumigatus* by Wallwey *et al.* An easD homologue from *Arthroderma benhamiae* was heterologously expressed and also oxidized chanoclavine-I in the presence of NAD⁺ to form chanoclavine-I-aldehyde.

The formation of ergoline ring D involves two enzymes, EasA and EasG, which are responsible for the cyclization of chanoclavine-I-aldehyde into either festuclavine (*A. fumigatus*) or agroclavine (*C. purpurea/N. lolii*). Homologues of EasA in the ergot cluster show protein sequence similarity to enzymes of the Old Yellow Enzyme (OYE) family. OYEs are responsible for the reduction of alpha beta unsaturated ketones and aldehydes, which initially suggested that these enzymes would be capable of reducing the alpha beta unsaturated carbons of chanoclavine-I-aldehyde to give the cyclized iminium intermediates in ring D formation (Figure 14.2).

A crucial difference between the ergot alkaloid classes is the fully saturated D ring of the clavine type alkaloids compared to the unsaturated ergoline D ring of the ergotamine type alkaloids. As opposed to the EasA homologue from *A. fumigatus*, which forms festuclavine, an EasA from *N. lolii* is involved in production of agroclavine and acts as an isomerase. A mutant of EasA which is capable of producing both festuclavine and agroclavine products confirms this critical branch point in ergot alkaloids biosynthesis.

The EasG protein encoded by the cluster displays similarity to Rossman fold NADPH reductases and its function is to reduce the proposed cyclized iminium products of EasA to form festuclavine (*A. fumigatus*) or agroclavine (*C. purpurea/N. lolii*).

### 14.4.4 Late Ergot Alkaloid Biosynthetic Enzymes

The early pathway of ergoline ring biosynthesis is defined by agroclavine or festuclavine production. Late pathway enzymes, which vary among different fungi species, are associated with biosynthesis of diverse alkaloid profiles. Transformation of agroclavine into ergopeptides is observed in the *Clavicipitaceous* fungi *C. purpurea* and *N. lolii*. The late-pathway biosynthetic genes in these organisms encode non-ribosomal peptide synthase (NRPS) domains. These genes have been studied by both gene disruption and in vitro characterization (Figure 14.4). It has been demonstrated that ergopeptide formation occurs via an enzyme complex composed of NRPS subunits D-lysergyl peptidyl synthetase (Lps2) that activates lysergic acid, and (Lps1) that forms the tripeptide moiety. The enzyme CloA was also demonstrated to be crucial for the oxidation of elymoclavine to paspalic acid. This enzyme oxidizes paspalic acid, which in turn forms...
Figure 14.4 Late ergot biosynthetic pathway. Ergotamine 5 derives from agroclavine 1 and fumigaclavine C 17 derives from festuclavine 2.
lysergic acid 20 either spontaneously or via an isomerase rearrangement (Figure 14.4).\textsuperscript{71} Recently, easH from \textit{C. purpurea} was heterologously expressed and characterized by Havemann \textit{et al.} This enzyme is annotated as a nonheme-iron dioxygenase, which cyclizes dihydrolysergyl-Ala-Phe-Pro-lactam to dihydroergotamine.\textsuperscript{72}

In contrast, conversion of festuclavine 2 into fumigaclavine A 22, B 21 and C 17, is carried out by the \textit{A. fumigatus} biosynthetic gene cluster. The late ergot pathway genes of this cluster have been demonstrated to show acetylation and reverse prenyl transferase activities.\textsuperscript{73,74} \textit{A. fumigatus} does not appear to harbour any genes that encode NRPS domains such as the ones observed in ergot biosynthetic clusters of \textit{N. lolii} and \textit{C. purpurea} (Figure 14.4). However, the nonribosomal peptide synthetases PesL and Pes1, previously believed to be involved in biosynthesis of fungal quinazoline derived natural products, have been shown to be essential for fumigaclavine C (17) biosynthesis in \textit{A. fumigatus} by gene deletion experiments.\textsuperscript{75} Notably, these synthetases are not found in the core ergot cluster. \textit{A. fumigatus} also produces fumitremorgin B, which requires an additional \textit{N}-prenylation step in addition to the one catalyzed by DmaW.\textsuperscript{76}

### 14.5 Production of Ergot Alkaloids \textit{De novo}

Production of ergot alkaloids in \textit{A. fumigatus} is limited to conidiating cultures.\textsuperscript{77} Cultures typically accumulate several pathway intermediates, with most of the alkaloid content associated with the fungal colonies, and are not exported to the media. Therefore, the native hosts are not always amenable for large-scale production of these compounds. A two-stage culture process including shake culture and static culture was shown to increase the production of fumigaclavine C (17) to 60 mg L\textsuperscript{-1}.\textsuperscript{78,79} Hulvova \textit{et al.} have recently described the challenges and progress in the use of \textit{Claviceps} as a source for biotechnological production of ergot alkaloids.\textsuperscript{80} Very recently, heterologous reconstitution of biosynthetic pathways reveals another option for expression of the ergot alkaloids.

Genes of the early steps of this pathway – dmaW, easF, easE, easC – have been reconstituted in \textit{Aspergillus nidulans} (a non-producer of ergots)\textsuperscript{81} and in \textit{Saccharomyces cerevisiae}, resulting in \textit{de novo} production of the chanoclavine-I 13.\textsuperscript{11} Finally, a recent review of Wallwey \textit{et al.} highlights the methods of production, detection and purification of clavine-type ergot alkaloids.\textsuperscript{82}

### 14.6 Chemical Synthesis of Ergot Alkaloids

Ergot alkaloids are also highly interesting and challenging targets for the organic chemistry community. A number of synthetic studies relied on a stepwise approach for construction of the C/D ring system, particularly of lysergic acid 20 – a crucial intermediate in the EA biosynthetic pathway.\textsuperscript{83–90} Oppolzer and co-workers reported another strategy based on simultaneous construction of the C and D rings \textit{via} an intramolecular imino-Diels-Alder
Recently, Kalinin et al. have reported C/D ring synthesis by intramolecular Heck and ring-closing metathesis reactions. The total synthesis of lysergic acid 20 and its derivatives, lysergol 23, isolysergol 24 and ergonovine 25 has been reported (Figure 14.5). Based on palladium-catalyzed domino cyclization of amino allenes bearing a bromoindolyl group, both racemic and enantioselective approaches to obtain lysergic acid 20, lysergol 23 and isolysergol 24, have been accomplished.

Very recently, the synthesis of cycloclavine – an unusual ergot alkaloid containing cyclopropyl ring – has been reported. The formal synthesis of (±)-cycloclavine (27) was carried out in seven steps and 27% overall yield from the known 2-(4-bromo-1-tosyl-1H-indol-3-yl)acetaldehyde (26). Key steps include an iron(III)-catalyzed aza-Cope-Mannich cyclization and an intramolecular Heck reaction or a self-terminating 6-exo-trig aryl radical–alkene cyclization (Figure 14.6).

The total synthesis of cycloclavine 27 was achieved in 14 steps, with a 1.2% overall yield. The crucial features of this synthesis include rapid construction of the heterocyclic core segments by two Diels-Alder reactions. An indole annulation was achieved by a late-stage intramolecular Diels-Alder furan cycloaddition, and a methylenecyclopropane dienophile was used for a stereoselective intramolecular [4 + 2] cycloaddition to give the cycloprop[a]indoline building block.

An important aspect of the chemical synthesis of these alkaloids is the synthesis of mechanistic probes, including the synthesis of isotope labelled building blocks for feeding experiments. For example, pioneering studies by Floss and co-workers showed that the origin of oxygen atoms in chanoclavine-I 13 and elymoclavine 18 was molecular oxygen. In addition, the mechanistic basis of ring C formation was investigated using synthetic probes by introducing a tritium label on α-carbon of L-tryptophan 7a, [13C2H3]methionine and an isotopic label on C-2 of DL-mevalonic acid. These studies also concluded that the oxygen atoms in 13a and 18a (Figure 14.7)
derive from molecular oxygen. Moreover, this work suggested that formation of ring C proceeds via carbocation formation at the benzylic position and formation of a carbanion at the α-carbon of the alanine side chain. The tritium label at the α-carbon of L-tryptophan has confirmed the hypothesis that the decarboxylation step has to occur prior to or simultaneous with ring C closure as this α-hydrogen has retained (Figure 14.7).

The chemical synthesis of natural products such as ergot alkaloids is challenging and expensive due to the complex structures of these molecules, which contain multiple stereogenic centres. The yields from total synthesis are relatively low, making biosynthesis and semi-synthesis a promising approach to obtain high yields of these bioactive molecules.

14.7 Application of Ergoline Scaffold in Medicinal Chemistry

Historically, the abusive uses of ergot alkaloids have overshadowed the beneficial medicinal properties of these compounds. The first clinical applications of EA were mentioned in 1100 BC in China, followed by a recurrence in medicinal usage in the early 19th century (see Section 14.1). Ergot-derived medicines were used to facilitate obstetric deliveries or to treat
Figure 14.7 Isotopic labelling studies that provide insight into the origin of oxygen atoms of chanoclavine-I 13 and elymoclavine 18. Additional $^{13}$C, $^3$H, and $^2$H labelling enabled a mechanistic hypothesis for ring C formation to be proposed.
postpartum haemorrhage (ergometrine). Intensive research on the oxytocic activity of ergots resulted in the synthesis of lysergic acid diethylamide (LSD) 3 in 1938 (Figure 14.1), the most hallucinogenic compound yet discovered. 3 LSD 3 has become infamous for its use as an illicit recreational drug. However, ergot alkaloids are also the inspiration for a wide range of semi-synthetic derivatives that find wide-ranging medicinal application as treatments for migraine (methysergide 4, ergotamine 5), parkinsonism (bromocriptine 6, cabergoline, pergolide), tumour (ergotamine 5) or restless leg syndrome (cabergoline, pergolide) (Figures 14.1 and 14.8).

The high bioactivity of ergot alkaloids is correlated with the ability of these compounds to act as agonists or antagonists toward neuroreceptors for dopamine, serotonin and adrenaline.17,98,99 In 2010, the production of these alkaloids was approximately 20,000 kg, of which field cultivation contributed about 50%. 80 Semi-synthetic derivatives of ergot alkaloids aim to tailor their potent bioactivity toward specific receptors, reducing adverse side effects. Therefore, the ergoline scaffold is one of the most important in terms of its application in medicinal chemistry. An ability to harness the biosynthetic pathways of these compounds will only enhance our ability to produce greater numbers of EA analogues that may have new and improved bioactivities.

References


