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Research review paper

Parasitic fungus *Claviceps* as a source for biotechnological production of ergot alkaloids

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ABSTRACT

Ergot alkaloids produced by the fungus *Claviceps* parasitizing on cereals, include three major groups: clavine alkaloids, D-lysergic acid and its derivatives and ergopeptines. These alkaloids are important substances for the pharmatech industry, where they are used for production of anti-migraine drugs, uterotonics, prolactin inhibitors, anti-Parkinson agents, etc. Production of ergot alkaloids is based either on traditional field cultivation of ergot-infected rye or on submerged cultures of the fungus in industrial fermentation plants. In 2010, the total production of these alkaloids in the world was about 20,000 kg, of which field cultivation contributed about 50%. This review covers the recent advances in understanding of the genetics and regulation of biosynthesis of ergot alkaloids, focusing on possible applications of the new knowledge to improve the production yield.

Contents

1. Introduction

The *Clavicipitaceae* family includes, among others, a fungal species called ergot that is important for humankind, in terms of both contributions and losses. In medieval history, these fungi parasitizing in cereals and producing a range of ergot alkaloids caused many mass poisonings that resulted in painful deaths of tens of thousands of people (Schiff, 2006). Nowadays, mass poisonings with ergot alkaloids are sporadic and occur only in developing countries. For example, an epidemic of ergotism with a high mortality rate occurred in 1977 in Ethiopia (Demeke et al., 1979). Contrary to mass poisonings, the recent cases of individual poisonings are usually connected with overdoses of medical drugs based on these alkaloids.

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For thousands of years, people tried to take advantage of substances produced by ergot without knowing their chemical structure, proper dosage or side effects, but scientific research on ergot alkaloids started only with the beginning of modern pharmacy in the early 20th century. Nowadays, specific types of ergot alkaloids are widely used as a basic drug-stock for the production of various therapeutic substances, e.g. for the treatment of migraine, in gynecology for its uterotonic effects, as prolactin inhibitors, antiparkinsonian drugs, etc. (de Groot et al., 1998).

The *Claviceps* genus is not only interesting for its ability to produce secondary metabolites usable in pharmaceutical industry, but also in its life strategy, mainly the specificity of invaded host organs, which is in the center of interest of many scientific groups. Last, but not least, its negative influence in agriculture should be mentioned. Some of the *Claviceps* species cause significant losses in cereal production. Recently, there was an infection of the fifth most important cereal crop in the world, *Sorghum bicolor* (Haarmann et al., 2009), by *Claviceps africana*.

2. Ergot alkaloids

2.1. History of poisoning and use of ergot alkaloids

First references to ergot use can be found in early history. The oldest documentation of the positive effects of ergot alkaloids in obstetrics appeared in China in approximately 1100 BC (Schiff, 2006). In one of the sacred books of the Parsees (400 BC to 300 BC), ergot is mentioned as "noxious grasses that cause pregnant women to drop the womb and die in childbirth" (Thoms, 1931). In the Middle Ages, there were many documented cases of mass intoxication with ergot caused by contaminated cereals, usually referred to as ergotism. There are two types of ergotism, which differ in symptoms. The first one, called "convulsive ergotism", was typical for the area located east of the Rhine river in Europe and was accompanied by muscle spasms, hallucinations and fever. These symptoms are typical for serotonergic stimulation of the central nervous system, caused by the activation of serotonin receptors by ergot alkaloids, due to their structural similarity to the neurotransmitter serotonin (Eadie, 2003). The second type of ergotism, typical for the area west of Rhine, is called "gangrenous ergotism", and is accompanied by violent burning and shooting pain of the affected acral part of the human body. Related to the saint who suffered horrible visions sent by the devil, this type of ergotism has been called St. Anthony's fire (Lee, 2009). The first documented epidemic of ergotism is dated 944–945 AD and caused the death of about 10,000 people in France. Some 50 years later, intoxication with ergot alkaloids again killed about 40,000 people in this area. It is likely that ergot alkaloid intoxication was also connected with the well-known witch trials of 1692 in Salem, Massachusetts, USA (Caporael, 1976; Spanos and Gottlieb, 1976) and in Finnmark, Norway in the 17th century (Alm, 2003). A correlation between the symptoms of ergotism and ergot consumption was understood finally in the 1850s, due to the findings of Louis René Tulasne, a French mycologist, who first fully described the life cycle of ergot (Tulasne, 1853). Modern ergot alkaloid research started in 1918 with ergotamine isolation by the Swiss biochemist Arthur Stoll (Stoll, 1945). In 1926, Swiss psychiatrist Hans Maier suggested that ergotamine might be useful in the treatment of vascular headaches of the migraine type (Silberstein et al., 2001). LSD, a synthetic derivative of lysergic acid, is one of the components of ergot alkaloid blend that was first synthesized in 1938 by the Swiss chemist, Alfred Hoffman, but its effect on nervous system was not discovered until he accidentally contaminated himself and experienced the hallucinogenic reaction in 1943 (Minghetti and Crespi-Perellino, 1999). The drug became popular in the mid-1960s when its sense-altering properties were reputed to offer a window into enhanced creativity and self-awareness.

2.2. Chemistry and occurrence of ergot alkaloids

Ergot alkaloids belong to the class of indole derivatives. They can be divided into three major groups: clavine alkaloids, D-lysergic acid and its simple derivatives and ergopeptines. Structures of typical ergot alkaloids are shown in Fig. 1. Species within the genus *Claviceps* differ in their capability to produce diverse types of alkaloids. Only a few species (e.g. *Claviceps purpurea* and *C. africana*) can produce ergopeptines as final products of their ergot alkaloid biosynthetic pathway. For example, the biosynthetic pathway of *Claviceps fusiformis* ends with elymoclavine production that has been explained as a loss of the late pathway genes in the ergot alkaloid gene cluster (Lorenz et al., 2007).

Most of ergot alkaloids contain a tetracyclic ergoline structure, although some of the naturally occurring clavine alkaloids are tricyclic, e.g. chanoclavine-I, chanoclavine-II and isochanoclavine-I (for a review see Buchta and Cvak, 1999). Of these, only chanoclavine-I can serve as a precursor for biosynthesis of other ergot alkaloids. Tetracyclic clavine

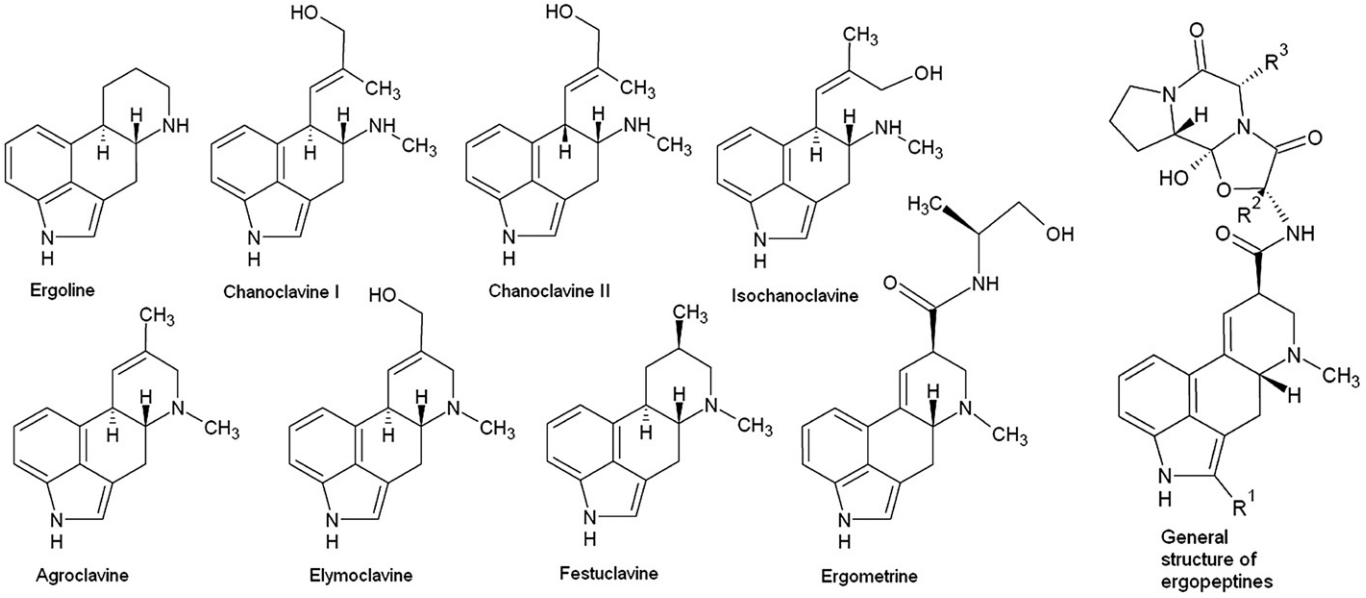

Fig. 1. Structures of ergot alkaloids.