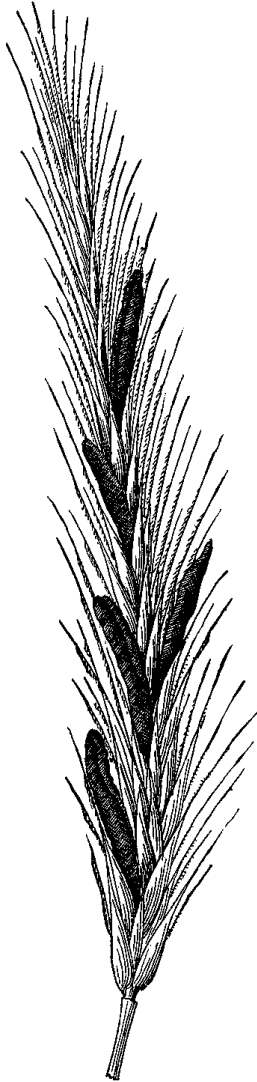




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Ergotism and ergot alkaloids – a review

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Uppsala, autumn 2003

Essay in Pharmacognosy – 10 credit B-level course in Pharmacognosy

Abstract

The grass-parasitic ascomycete; ergot (*Claviceps purpurea* (Fr.) Tul.), contains numerous terpenoid indol alkaloids, some of which has dramatic physiological effects and are of great medicinal value. During the Medieval Ages, ergot infection of rye (*Secale cereale* L.) was a cause of extensive epidemics with high mortality rate, characterised by painful convulsions and gangrene of limbs. Ergot extracts have been used in traditional medicine for a long time, and several isolated specific alkaloids as well as semi-synthetic derivatives of these have proved to be useful remedies in modern medicine. Ergot alkaloid amide and peptide derivatives have a wide variety of physiological effects, including serotonin- and dopamine-receptor agonists and antagonist, vasoconstrictors, neurotoxins and hallucinogens. This essay gives a short literature review of the history, biochemistry and medical applications of ergot.

Introduction

Ergot is the sclerotium (resting stage) of parasitic ascomycetes of the genera *Claviceps*, notably *C. purpurea* (Fr.) Tul. (*Clavicipitaceae*), which replace the seeds of susceptible grasses, commonly rye (*Secale cereale* L.). In spring the sclerotium; a 1-3,5 cm long, cylindrical, brown or blackish, dense tissue of hyphae, forms ascospore fruit bodies. The spores are wind dispersed, and upon germination on a developing grass seed, the formed hyphae may penetrate and destroy the seed ovary, replacing them with a new sclerotium. The sclerotia can now produce conidiospores and a sticky, sugar containing secretion that attracts insects, allowing further dispersal to new hosts before it falls to the ground in the autumn to hibernate until next spring, completing its life cycle (Ryman & Holmåsén, 1992). A cold winter followed by a wet spring favours germination. Ergot on rye has been very common in Europe, with the cool, damp growing conditions common in France and Germany promoting fungal growth (Hart, 1999). Its influence on society is indicated by the complex native nomenclature, with 25 names in French, 62 in German, 21 in Dutch, 15 in the Scandinavian languages, 14 in Italian and 7 in English (Schultes and Hofmann, 1992).

During the Medieval Ages, midwives used ergot for medical applications, where a small dose could be used to hasten labour or prevent postpartum bleeding (Hart, 1999). The impurities and quantitative and qualitative differences of the extracts did however restrict its use in modern medicine (Tudzynski *et al.*, 2001), although it was used in Germany and USA to treat “vascular headache” such as migraine until the late 19th century (Hart, 1999). During this time physicians in the USA also began to use ergot for obstetric purposes, but soon realised that this increased the risk of stillbirth, and restricted the administration to after delivery to prevent haemorrhage (Eadie, 2003). Ergot contains numerous neurotoxic and vasoconstrictive alkaloids, with the latter accounting for both the gangrenous form of ergot poisoning and ergot’s medical applications in preventing haemorrhage and treating migraine headache. (Hart, 1999).

Consumption of rye bread contaminated with ergot was responsible for epidemics of ergot poisonings (ergotism) that occurred in the past. Early reports recognised two main forms of epidemic ergotism: a “gangrenous” form and a “convulsive” form, although these could occur concurrently (De Costa, 2002; Eadie, 2003). In France and other European countries west of the Rhine, outbreaks of ergotism were typically of the gangrenous type, whereas in central and eastern Europe and Scandinavia, outbreaks were normally of the convulsive type (Barger, 1931, cited by Eadie, 2003). It has been suggested that an associated vitamin A deficiency could be an additional causative factor in inducing convulsive ergotism, however no direct evidence in support of this hypothesis has emerged (Eadie, 2003).

The initial symptoms of the gangrenous and the convulsive forms are described as being similar. After a short period of vague illness, perhaps with some gastrointestinal symptoms, the first manifestation of the disorder was an abnormal sensation in the limbs, mainly the legs, which was described as feeling like ants crawling over the skin. Local pain then developed in the limbs. If the disorder progressed beyond this, the manifestations separated into two distinct patterns (Eadie, 2003). Gangrenous ergotism was characterised by ischaemia with some loss of sensation

of the limbs followed by an intense burning pain known as Holy Fire or St Anthony's Fire, and gangrene due to the vasoconstrictive properties of ergot. In severe cases, affected tissues became dry and black, and mummified limbs dropped off without loss of blood. Spontaneous abortion frequently occurred (De Costa, 2002). Gangrene could be complicated by secondary infection, and the mortality rate was high.

In convulsive ergotism the initial features included distortion of the trunk and limbs, painful involuntary flexion of the fingers and wrists, and either flexion or extension of the ankles. People with the disease were drowsy, sometimes delirious, lethargic, and melancholic or manic and could have hallucinations and double vision. Profuse sweating, fever, muscle stiffness, and twitching could also occur. As the disorder progressed, the trunk could become either extended rigidly or so bent by spasm that the body seemed to roll up into a ball. These painful postures could be lasting for minutes to hours, and reoccur after intervals of hours to days. In between recurrences, affected individuals might be capable of normal activities but were ravenous. Involuntary movements and postures were, in some cases, followed by epileptic seizures, which were indicative of a fatal outcome. The recovery phase was commonly associated with diarrhoea, sudden swelling of the hands, and blistering of the skin of the feet. Mortality was about 10–20% (Tissot 1840, cited by Eadie, 2003). Repeated epidemics occurred throughout the Medieval Ages, when whole populations were affected by contaminated rye bread. Ergot was however not identified as the cause until 1630 (Eadie, 2004). There have been suggestions that the alleged outbreaks of witchcraft in New England, especially Salem, Massachusetts, may have been due to (convulsive) ergot poisoning (Schultes and Hofmann, 1992). The last reported European outbreak, with more than 200 cases and 4 deaths, occurred in 1951 in a French village (Hart, 1999), and *C. purpurea* infected wild oats caused an outbreak of the gangrenous form with 93 cases and 47 deaths in Ethiopia as recently as 1977 (Demekke *et al.*, 1979).

Today, cereals are mechanically cleaned of sclerotia, but this does not provide complete protection. Therefore contamination of flour with ergot alkaloids is still a problem, and has even increased lately, due to new rye varieties being less resistant to *C. purpurea* (Tudzynski *et al.*, 2001). Ergot alkaloids is also a problem to cattle, being present in the endophyte *Neotyphodium coenophialum* of the common fodder grass tall fescue (*Festuca arundinacea* Schreb.), and causing outbreaks of tall fescue toxicosis with a hyperthermia syndrome characterized by severe loss in milk production, loss of body mass and reduced fertility (Schneider *et al.*, 1996; Bush *et al.*, 1997).

Ergot alkaloids

Ergot alkaloids are amides of the terpenoid indole derivate D-lysergic acid, and are produced by a wide range of fungi, predominantly the *Clavicipitaceae*, but are also present in members of the plant family *Convolvulaceae*, e.g. *Ipomoea violacea* and *Turbina corymbosa* (Samuelsson, 1999; Tudzynski *et al.*, 2001). More than 50 ergot alkaloids have been isolated from ergot, of these those derived from isolysergic acid (with names ending with –inine) are pharmacologically inactive, but may in an aqueous solution isomerise to produce an equilibrium mixture with pharmacologically active lysergic acid derivatives (names ending with –ine). Ergot alkaloids derived from lysergic acid can be divided into amide derivatives, peptide derivatives and clavines (Eadie, 2003). Ergot alkaloids are formed from condensation of tryptophan and isopentenyl diphosphate forming dimethylallyltryptophan (DMAT), followed by consecutive methylation, oxidation decarboxylation, ring closure, and further oxidation (Fig. 1, Samuelsson, 1999).

The pharmacological effects of the various ergot alkaloids and their derivatives are due to the structural similarity of the tetracyclic ring system to neurotransmitters such as noradrenaline, dopamine or serotonin (Fig. 2), and interaction with multiple receptors in these systems (Silberstein, 1997). The compounds have a wide spectrum of activities, and depending on the substituent attached to the C-8 carboxyl group of the ergoline ring, the affinity towards the neurotransmitters receptors vary; behaving as agonists or antagonists or playing a dual role as partial-agonist and antagonist. Ergot alkaloids exhibit a wide spectrum of biological action

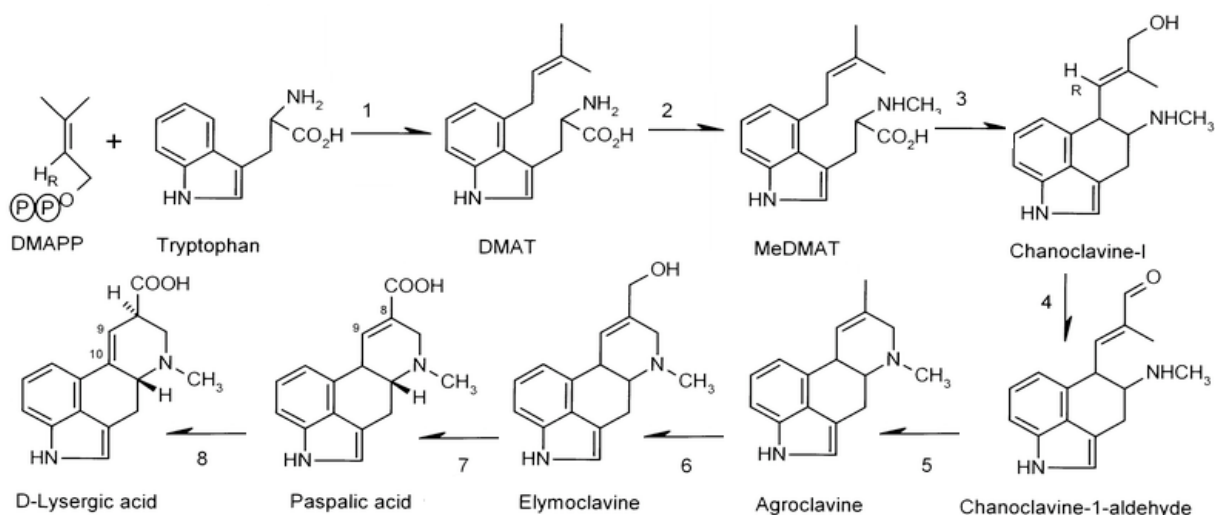


Figure 1: Pathway of ergoline ring synthesis up to the stage of D-lysergic acid. Image modified from Tudzynski *et al.* (2001).

(Mantegani *et al.*, 1999). The peptide ergot alkaloids exert vasoconstrictive and sympatholytic-adrenolytic effects due to their affinity for adrenergic receptors (see Tudzynski *et al.*, 2001 for references). By contrast, clavines which lack the carboxyl group and the simple D-lysergic acid amides with a small side chain such as ergometrine have much less adrenolytic activity and show strong anti-serotonergic action due to elevated affinity for serotonin receptors. The serotonin syndrome can be caused by binding of dihydroergotamine to serotonin receptors in the dorsal horn of the spinal cord, which is the site of neuropathological changes in convulsive ergotism (Eadie, 2003). In addition to interacting with dopamine receptors, several ergot alkaloids may produce dopaminergic effects by increasing the release of dopamine from central nerve endings. Ergocryptine, ergocristine, and bromocryptine produces an elevation in dopamine release of about 400%, whereas ergotamine, ergonovine, ergovaline, and ergocornine have no such activity (Rowell and Larson, 1999).

Structural alterations of the ergoline-ring as well as the introduction of unnatural side chains at the C-8 substituent have drastic effects on the compound properties. D-lysergic acid derivatives amidated with small amino-alcohols show high affinity for serotonin receptors, while bromination of ergocryptine in the 2-position strongly increases dopamine agonist activity (Tudzynski *et al.*, 2001). Hundreds of chemical modifications and synthetic variations of ergot derivatives have been prepared aimed at finding compounds with a narrower range of activity with more selective, more specific effect (Mantegani *et al.*, 1999). Ergot used for extraction of alkaloids is collected from mills, and in some countries inoculated and grown on rye. Demand is however increasingly being met by production in tank cultures similar to those used for production of antibiotics (Samuelsson, 1999).

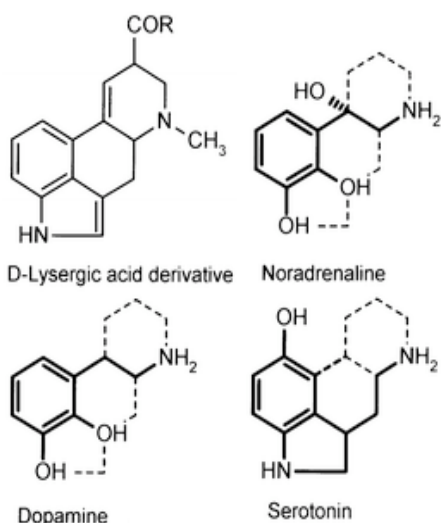


Figure 2: Structural analogy between the ergoline ring system and different neurotransmitters (dopamine, noradrenaline, serotonin). Image modified from Tudzynski *et al.* (2001).

Primary food preparation, as bread-baking reduces the total alkaloid contents by about 50%, with the pharmacologically active alkaloids being reduced to a much greater extent than the less active type (Wolff *et al.*, 1988). If the ergot has been soaked in water before ingestion, hydrophilic ergot alkaloids, such as ergometrine, tend to dissolve. In addition, the ergot alkaloids may undergo substantial presystemic elimination after oral administration (Eadie, 2003).

Important ergot alkaloids

Ergocryptine

Ergocryptine is an ergot alkaloid that affects dopaminergic activity principally by interacting with D2-type receptors (Rowell and Larson, 1999). The semisynthetic bromination derivative has increased dopamine agonist activity, and is used against Parkinsonism and to reduce growth hormone secretion and milk production (Samuelsson, 1999).

Ergotamine

Ergotamine was first isolated in 1918 and marketed as a safer and more reliable form than the ergot extracts. Controlled trials in the 1930s showed it to be efficient in relieving migraine headache (Hart, 1999), and prior to the various triptan derivatives of the past decade, was among the most effective available agents for relieving migraine attacks (Eadie, 2004). It is still widely used in some countries for the treatment of severe migraine attacks, and is generally regarded as a safe and useful drug if prescribed for infrequent use, in the correct dose, and in the absence of contraindications; however, safer and more effective options do exist in the triptans, as ergotamine abuse may cause ischaemia and even ergotism. (Bigal and Tepper, 2003).

Ergometrine (Ergonovine)

Ergometrine and the semi-synthetic methylergometrine have been widely used for the prevention and treatment of excessive uterine bleeding following birth, and also to initiate delivery. They can be however be unstable, and have side-effects including nausea, vomiting and hypertension, Nowadays the natural hormone oxytocin is the preferred drug (Hogerzeil and Walker, 1996; Samuelsson, 1999; De Costa, 2002).

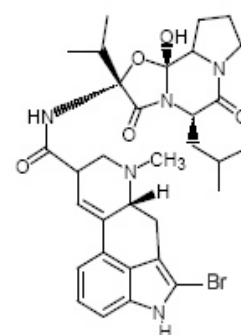
Lysergic acid diethylamide (LSD)

Lysergic acid (LSA) and its synthetic derivate lysergic acid diethylamide (LSD) are powerful hallucinogens, transiently altering human perception, behaviour, and mood already at very low doses. Under influence of LSD the personality disintegrates (Samuelsson, 1999). LSD is a serotonin receptor agonist, and temporary changes in 5-HT_{2A} mediated gene expression have been shown after administration of LSD (Nichols *et al.*, 2003). It can, however, also interact with dopamine receptors, and these interactions with several receptor subtypes implicated in both normal and abnormal human behaviours, makes it a useful tool for probing the biochemical basis for behaviour (Nichols and Sanders-Bush, 2002).

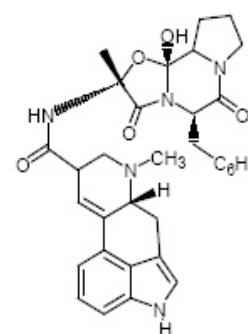
According to Harvey (2003) agonists of the 5-HT_{2A} receptor such as LSD may enhance associative learning at doses that produce cognitive effects in humans. At least some individuals who have used LSD, experience persistent perceptual abnormalities reminiscent of acute intoxication, not better attributable to another medical or psychiatric condition, which persist for weeks or months after last exposure (Halpern and Harrison, 2003).

Methysergide

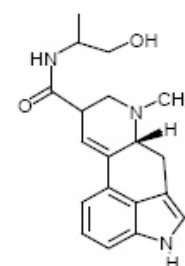
Methysergide is a semi-synthetic ergot alkaloid, which unlike ergotamine is a serotonin antagonist used in the treatment of migraine, and is used for daily preventive therapy rather than in acute cases. Possible side effects include “unworldly feelings” or hallucinations (Hart, 1999).



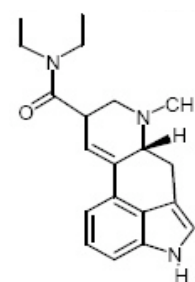
2-bromo- α -ergocryptine



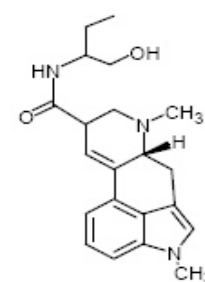
ergotamine



ergonovine



lysergic acid diethylamide



methysergide

Discussion

Ergot and ergot alkaloids have had medical importance for a long time. Structural similarities with several neurotransmitters and thus wide-scale physiological influence make this a very interesting group of metabolites for the development of future medicines. Especially in the understanding and treatment of psychological disorders there is a lot to be gained. Indeed large efforts are also made into finding better and more suitable derivatives, as well as economic ways of synthesising these. Economic interest also lies in the avoidance of ergot alkaloids, as poisoning of cattle by alkaloid producing grass endophytes in the diet may reduce the production and fertility of the animals. The combination of highly productive *Claviceps* strains, efficient tissue culture methods and the possibilities of biotechnology will likely increase the potential of these compounds in the future, and bring ergot yet another step away from the torments of the ergotism epidemics of the Medieval Ages.

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