HUMAN DEVELOPMENT AND ERGOT ALKALOIDS

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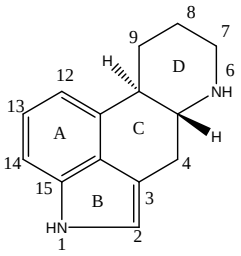
The ergot a1kaoids are one of the largest known groups of nitrogenous fungal metabolites. These alkaloids have been identified as the causative agent of St. Anthony's Fire which was the dreaded medieval gangrenous scourge. During the middle ages the therapeutic importance of ergot was first established. Its capacity to induce uterine contraction was recorded as early as 16th century. The crude preparations of this class of alkaloids were introduced into orthodox medicine early in the nineteenth century. The isolation and structural elucidation of pure active principles of ergot were accomplished during the middle twentieth century. Arthur Stoll played a dominant role in isolation of active substances from ergot. He worked for the isolation of bases all of which have been shown to be amides of the same key substance lysergic acid having a unique tetracyclic ring system named "ergoline".

Ergot alkaloids are characterized by the tetracyclic ergoline ring system or by related tricyclic alkaloids open between N (6) and C (7) (ergoline numbering). The trivial name “Ergoline” is given to fig. 1 below and the compounds containing ergoline have a fused indole which contains the double bond at C 9 - C 10 position and achiral center [1-2] at C 5 and C 8 position. 9, 10- Double bonded compounds related to lysergic acid is called a 9-Ergolene rather than a 9, 10-Didehydroergoline. The name D-Ergoline or D-8-Ergolene or D-9-Ergolene is used here in naming specific compounds. The letter “D” indicates that C-5 carbon atom configuration has the absolute sterero chemistry designated as R and that the hydrogen is beta above the plane of the ring system.



The natural ergot alkaloids have a broad spectrum of pharmacological activities including central, neurohumoral and peripheral effects.[3] Various ergot derivatives are used as drug of high potency in the treatment of disorders such as e.g. uterine atonia, postpartum bleeding, migraine, orthostatic circulatory disturbances, senile cerebral insufficiency, hypertension, hyperprolactenemia, acromegaly and parkinsonism.[5] The industrial synthesis of the most important ergot alkaloids available on the market (i.e. cabergoline, nicergoline, pergolide mesylate, bromocryptine and lisuride) are semisynthetically prepared from basic precursors e.g. lysergic acid and elymoclavine produced by fermentation of mutant of claviceps paspali and claviceps perpurea respectively. Agroclavine is the key intermediate for the synthesis of a number of ergot derivatives under clinical development e.g. setoclavine, lysergol, lysergene, [6] elymoclavine [7-8] festuclavine, pyroclavine, costaclavine [9]. Ergot alkoloids cover a broad range of therapeutic uses as the drug of high potency in the treatment of various disorders such as migraines, orthostatic circulatory disturbances, senile cerebral insufficiency, hypertension, acromegaly, parkinsonism [10] etc. In mammals, ergot alkaloids affect the central and sympathetic nervous systems, as well as immune and reproductive systems, resulting in symptoms such as muscle contractions, changes in blood pressure, lowered immune response, reduced lactation and reproductive capability, disturbances in sleep/wake cycles, hallucinations, and gangrene of the extremities. [11–12] Different ergot alkaloids exert their effects by acting in some cases as partial agonists or, in other cases, antagonists at receptors for 5-HT (5-hydroxytryptamine or serotonin), dopamine, and noradrenaline. [13-15] These alkaloids have been reported to exhibit broad biological activity, and several synthetic derivatives such as pergolide or bromocriptine are also used as antiprolactin and anti-Parkinson's disease drugs. [16] Elymoclavine has been shown to have potent rat prolactin inhibiting activity comparable to that found with peptide alkaloid ergocornine. It acts as partial

agonist and antagonist at Rat 5- H_{2A} receptors. Some EA show structural similarity to the neurotransmitters serotonin and dopamine and have affinity to the cognate receptors in the central nervous system. [17] Therefore, EA have long been used for treatment of a variety of disorders of the central and peripheral nervous systems.[18-19] Many ergot alkaloids have valuable properties and have found wide use in clinical practice in the treatment of a number of diseases. In particular, agroclavin has antimicrobial and cytostatic activities and agroclavine and its derivatives are thus regarded as potential compounds for therapeutic exploitation. [20-22] agroclavine possesses antibiotic activity against some pathogenic and apathogenic bacterial species [23-24] and remarkable cytostatic activity in the LSI78Y mouse lymphoma cell system. [25-26] Agroclavine, an alkaloid produced by some species of fungi and dicotyledon plants, and its alkylated derivatives are potentially useful as antineoplastic drugs, since they exert potent and selective cytostatic effects.

Animal experiments have shown that elymoclavine, agroclavine and lysergol exhibit excitatory effects on central nervous system as does LSD, suggesting that these substances may well be psychoactive in human as well. [27] Many therapeutically used ergot alkaloids belong to the peptide alkaloids but a significant number is semi synthetically prepared prepare whose production is based on few basic precursors e.g. lysergic acid, 9,10- dihydrolysergic acid, lysergol and elymoclavine. Therefore, potent and versatile physiological activities of ergot alkaloids prompted a thorough chemical and pharmacological investigation of the structure- activity relationship of this class of natural products.[28] In mammals, ergot alkaloids affect the central and sympathetic nervous systems, as well as immune and reproductive systems, resulting in symptoms such as muscle contractions, changes in blood pressure, lowered immune response, reduced lactation and reproductive capability, disturbances in sleep/wake cycles, hallucinations, and gangrene of the extremities.[29] . They are well known from their historical role in human toxicoses. In mammals, ergot alkaloids affect the central and sympathetic nervous systems, as well as immune and reproductive systems, resulting in symptoms such as muscle contractions, changes in blood pressure, lowered immune response, reduced lactation and reproductive capability, disturbances in sleep/wake cycles, hallucinations, and gangrene of the extremities. [30] Thus, the ergot alkaloid is an

important class of alkaloids and have been known to have its existence since many centuries. The detailed understanding of alkaloid synthesis is essential to improve production of alkaloids of interest. This discovery of new bioactive molecules will be helpful to sustainably exploit the drugs against targets of interest.

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