Ergot-Natural Fungus, Pharmocognosy and Utilization

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Abstract- *Students at the University of Pittsburgh receive an introduction to pharmacognosy and natural products during their first-professional year in an introductory course in Drug Development. The role of natural products as both historical and continuing sources of drugs, as well as sources of precursors for semisynthetic modification and sources of probes for yet undiscovered drug moieties, is emphasized. In addition, students are continually exposed to the concept that complex natural products are a result of secondary metabolism, and as such are produced via the unique combination of a relatively limited number of structurally unsophisticated primary metabolites. As a consequence, secondary metabolites have a more limited distribution in nature, and their occurrence is an expression of the individuality of the parent species. This curricular dialog with pharmacognosy and various bioactive natural products continues in courses in the second-professional year [Pharmacotherapy of Infectious Disease 1 and 2 Cardiology) and third-professional year (Oncology, Pulmonology & Rheumatology, Neurology/Psychiatry).*

I. EARLY HISTORY[1-11]

Although it has been speculated that the 4,000-year old Eleusinian Mysteries of ancient Greece were connected with ergot-induced hallucinations, the earliest authenticated reports of the effects of ergot occurred in Chinese writings in approximately 1100 BC, when the substance was used in obstetrics. A magic spell found in a small temple in Mesopotamia dating to 1900-1700 BC referred to abnormally infested grain as *mehru*, while Sumerian clay tablets of the same period described the reddening of damp grain as *samona*. The Assyrians of this era were sufficiently knowledgeable to differentiate between different diseases affecting grain and by 600 BC writings on an Assyrian tablet alluded to a "noxious pustule in the ear of grain." References to grain diseases have also been found in various books of the Bible in the Old Testament (850-550 BC). In 550 BC the Hearst Papyrus of Egypt described a particular preparation in which a mixture of ergot, oil, and honey was recommended as a treatment for hair growth. In 370 BC Hippocrates furnished a description of corn blight and subsequently described ergot as*melanthion*, noting its use to halt postpartum hemorrhage. Around 350 BC the Parsi wrote of "noxious grasses that cause pregnant women to drop the womb and die in childbed," while in 322 BC Aristotle postulated that grain rust was caused by warm vapors. Around 286 BC the Greeks concluded that barley was more susceptible than wheat to rust infections, and that windy fields had less rust than damp, shady low-lying ones.

II. MIDDLE AGES TO TWENTIETH CENTURY[1-11]

The first documented epidemic of *ergotism* likely occurred in 944-945 AD, when some 20,000 people of the Aquitane region of France (about half of the population) died of the effects of ergot poisoning. Some 50 years later, about 40,000 people reportedly died because of the "holy fire."

Up through the 18th Century botanists persisted in considering ergot to be a "super" rye, possessing an enlarged kernel. Finally, in 1764, ergot was recognized as a fungus by von Munchhausen. Epidemics of ergot poisoning, often termed *ergotism*, continued to ravage continental Europe through the Middle Ages and outbreaks of ergotism occurred in Germany in 1581, 1587, and 1596. These epidemics were due, in part, to the fact that rye was grown in larger quantities in medieval times, and many people (particularly those less wealthy) ingested contaminated rye flour.

These outbreaks were characterized by the production of 2 distinct forms of toxic reactions, with these reactions now being understood to be attributable to the effects of the alkaloids produced by the parasitic ergot fungus which was contained within the ergot fungal body (sclerotium). The fungus-contaminated grain crops along with their fungal metabolites (ergot alkaloids) were ingested with flour prepared from the grain. The first gangrenous form (*Ergotismus gangraenosus*), commonly known as "holy fire," "infernal fire," or "St. Anthony's Fire," was more common in France and its effects were characterized by pronounced peripheral vasoconstriction of the extremities (limbs). Hands, feet, and whole limbs would swell, producing a violent, burning pain that ultimately culminated in the separation of a dry gangrenous limb (usually a foot) at a joint, without pain or loss of blood. St. Anthony's Fire was so named because the Order of St. Anthony traditionally cared for sufferers in the Middle Ages, and the condition was characterized by severe burning pain ("fire"). The second form of ergotism, also known as the convulsive form (*Ergotismus convulsivus*), was

particularly common in Germany and was typically characterized by the development of delirium and hallucinations, accompanied by rigid, extremely painful flexed limbs, muscle spasms, convulsions, and severe diarrhea.

The term *ignis sacer* (holy fire) was commonly employed for epidemics of ergotism, but numerous other terms, mainly of Latin derivation, were coined, including: *Ignis judicalis, Ignis occultus, Morbus hic tabificus, Mortifer ardor, Pestilens ille morbus, Pestis ignaria, Plaga ignis, Plaga illa, and Plaga invisibilis.* Many were quite naturally translated into various European languages, including French (*Feu sacré*) and German (*heilige Feuer*). Other terms for ergotism included names of regions (*Mal de Cologne*) and of saints to whom an appeal for help was made (St. Anthony, St. Martin, St. Martial).

In 1597 scientists at Marburg University observed that signs of ergotism often appeared after blighted rye grains were consumed, and that blight was promoted by cold, damp growing seasons. In 1630 it was observed that feeding of blighted grain to animals produced an illness similar to human ergotism and by the end of the 18th century poisoning was demonstrated in animals. Although the source of ergotism was linked to the consumption of infected rye by 1676, it was the large outbreaks of ergotism in Europe in 1770 and 1777 that prompted the introduction of legislation in France and elsewhere. Epidemics of gangrenous ergotism were recorded from the Middle Ages to the nineteenth century, while that of convulsive ergotism were documented between 1581 and 1928.

III. TWENTIETH CENTURY[1,12]

From 1926 to 1927, some 11,319 cases of ergotism were reported in a population of 506,000 in the vicinity of Sarapol, near the Ural mountains. In 1928, 200 Jewish refugees in Manchester, England, were sickened when they consumed rye bread that had been prepared from rye grown in South Yorkshire. In mid-August of 1951, 230 villagers of the popular French tourist town of Pont Saint-Esprit on the Rhone River were sickened after ingesting contaminated goods from a local baker. They became violently ill with symptoms of severe gastrointestinal upset, dramatic reduction in body temperature, hallucinations, euphoria, and suicidal ideation. Within days, some became extremely delirious and others complained of excruciating burning pains in the extremities, culminating in the development of gangrene in some patients.

IV. EARLY MEDICINAL USES[1,2,13]

In 1582 a preparation of ergot that was employed in small doses by midwives to produce strong uterine contractions was described by Adam Lonicer in his *Kreuterbuch.* The use of ergot as an oxytocic in childbirth became very popular in France, Germany, and the United States. The first use of the drug in official medicine was described by the American physician John Stearns in 1808, when he reported on the uterine contractile actions of a preparation of ergot obtained from blackened granary rye as a remedy for "quickening childbirth." However, shortly thereafter the number of stillborn neonates rose to a point that the Medical Society of New York initiated an investigation. As a result of this enquiry, it was recommended in 1824 that ergot only be used in the control of postpartum hemorrhage. Ergot was introduced into the first edition of the *United States Pharmacopeia* in 1820 and into the *London Pharmacopeia*in 1836.

V. LIVESTOCK POISONING[14]

Ergot alkaloid contamination of livestock feeds has long been known and has been described in various places. Although reports of ergotism in livestock vary from year-to-year in the United States according to rainfall and temperature, this mycotoxicosis occurs in the grain-producing areas of the Northern plains in most years. Three syndromes have been described in animals: nervous ergotism, gangrenous ergotism, and agalactia.

Go to:

VI. BIOLOGY AND CHEMISTRY[3-5,9,13,15,16]

Biology and Lifecycle

The genus *Claviceps* is a group of phytopathogenic ascomycetes that is composed of approximately 36 different species of filamentous fungi. These species are known to parasitize over 600 monocotyledonous plants of the families Poaceae, Juncaceae and Cyperaceae, including forage grasses, corn, wheat, barley, oats, millet, sorghum, rice, and rye. Ergot was first recognized as a fungus in 1711 but its lifecycle was not described in the form of a general outline until 1853 by Tulasne. The term ergot or *Secale cornutum* derives from the French word *argot* (a spur) and represents the dark brown, horn-shaped pegs that project from ripening ears of rye in place of rye grains. These tuberous projections are collected before and during harvesting or are separated from the threshed rye. In a histologic sense, these bodies consist of compactly interwoven hyphae of the filamentous fungus *Claviceps purpurea* (Fries) Tulasne but biologically these compact grains are designated as sclerotia, the form in which the fungus passes the winter.

The parasitic life cycle of the ergot fungi begins in the spring, with wind-borne ascopores landing on susceptible host plants. Hyphae invade and colonize the ovary, producing masses of anamorphic spores that are exuded into a syrupy fluid (honeydew). Insect vectors, rainsplash, or head-to-head contact transfer this honeydew to other blooming florets, allowing the spread of the ergot fungi in a field. When the sclerotia begin to form, production of honeydew and condiation cease, and the sclerotia mature in about 5 weeks. The number and size of sclerotia produced on each spike of cereal by *C. purpurea* varies according to grain, with rye usually bearing a considerable number, while wheat has relatively few. The sclerotia are considered as the early stage of sexual differentiation of *Claviceps*. In autumn, the ripe pigmented sclerotium leaves the spike and falls to the ground, ultimately producing asci and nonseptate ascospores, thereby completing the cycle.

Sources of Ergot Alkaloids [4,5,9,17-19]

The industrial production of the ergot alkaloids began in 1918 when Arthur Stoll patented the isolation of ergotamine tartrate, which was subsequently marketed by Sandoz in 1921. Sandoz dominated the world industrial market in ergot alkaloid production up until the 1950s, when other competitors begin to appear. Today Novartis (the successor to Sandoz) still retains leadership in the world production of ergot alkaloids. Some other major producers of these alkaloids market their products as bulk pharmaceutical chemicals, including: Boehringer Ingelheim (Germany), Galena (Czech Republic), Gedeon Richter (Hungary), Lek (Slovenia), and Poli (Italy). Others active in the marketplace include Eli Lilly and Farmitalia. Annual world production of ergot alkaloids has been estimated at 5,000-8,000 kg of all ergopeptines (peptidic ergot alkaloids) and 10,000-15,000 kg of lysergic acid, the latter being mainly used in the manufacture of semisynthetic derivatives. The greater part of this production occurs as a result of fermentations (around 60%) while field cultivation of tritcale (a hybrid of wheat and rye) accounts for the balance.

Chemistry of Ergot Alkaloids[4,5,7,9,20]

The ergot alkaloids are indole compounds that are biosynthetically derived from L-tryptophan and represent the largest group of nitrogenous fungal metabolites found in nature. Over 80 different ergot alkaloids have been isolated, mainly from various *Claviceps* species (over 70 alkaloids), but also from other fungi and from higher plants. Ergot sclerotia contain about 0.15%-0.5% alkaloids, with the medicinally useful compounds separated into 2 classes: the water-soluble amino alcohol derivatives (about 20% of the total alkaloid mixture) and the water-insoluble peptide derivatives (up to 80% of the total alkaloids). A common portion of the ergot alkaloids is a tetracyclic ring system assigned the trivial name of *ergoline*, which is a partially hydrogenated indole[4,3-f,g]quinoline. These alkaloids may be conveniently divided into 3 major structural groups: clavines, lysergic acid amides (paspalic acid amides), and peptides (sometimes designated ergopeptides or ergopeptines).

The nomenclature of this group of alkaloids is quite complex, with the naturally occurring compounds commonly being assigned a trivial name by their discoverer(s). Systematic names tend to be used only for semisynthetic derivatives or to ascribe an exact chemical description of the molecule. Many of the trivial names of these alkaloids are derived from the botanical names of the host plant or producer, as ergosecaline (*Secale spp*). Still others are a product of special circumstances of their discovery, such as ergokryptine, an alkaloid that remained elusive (*cryptic*; *kryptos* [Gr]) and obscured for many years. Ergobasine was so named because of its basic properties, while lysergic acid received its name because it was a product of the lysis of various ergot alkaloids. Some alkaloids bear nomenclature that reflects specific pharmacological properties, such as ergometrine for its actions on the uterus (endometrium uteri). Still other alkaloids have been named to reflect some personal attachment, such as ergocristine for Cristine Stoll, daughter of the scientist Arthur Stoll who isolated ergotamine and later was President of Sandoz AG in Basel, Switzerland.

There have been 3 forms of systematic nomenclature reflecting different chemistry that are employed for the alkaloids of this group. The first utilizes a system found in chemical abstracts that employs ergoline as the name for the tetracyclic system present in most ergot alkaloids and ergotaman for the heptacyclic system occurring in most of the peptidic alkaloids. The second type employs the name ergopeptine, and is used only for the full heptacyclic peptidic alkaloid system. The final type utilizes the IUPAC system, and as such is the most rigorous and rational, albeit complicated. In this variation, the ergoline system is designated as 7-methyl-4,6,6a,7,8,9,10,10a-octahydro-indolo[4,3-f,g]quinoline.

Ergot alkaloids contain several centers of chirality of varying configuration, but the R- chirality at C-5 is constant and nonvariable, reflecting the derivation of these alkaloids from L-tryptophan (the amino acid precursor of the indole ring) as well as the C-4, C-5, and N-6 atoms. The medicinally useful ergot alkaloids are all C-8 amide/peptide derivatives of (+)-lysergic acid, a compound bearing the R-chirality at C-8.

Clavine Ergot Alkaloids

The clavines are substituted 6,8-dimethylergolines but include a few members, such as the chanoclavines, that possess a 6,7-seco D-ring. Although at least 35 alkaloids of this type have been isolated and characterized, none of the group is used medicinally.

Lysergic Acid Amide Ergot Alkaloids

Amidation of the C-8 carboxy-group of lysergic acid results in the formation of 2 types of compounds: the simple nonpeptidic amides that bear relatively short carbon chains and the peptidic amides that commonly exist as tripeptides. Common 5R,8R-nonpeptidic amides found in ergot include ergonovine (ergometrine, ergobasine), lysergic acid 2-hydroxyethylamide, lysergic acid amide (ergine), and paspalic acid. Lysergic acid-derived amides are highly active pharmacologically, and ergonovine and its semisynthetic derivatives methylergonovine and methysergide are used medicinally. As a consequence of the adjacency of the C-8 chiral carbon of lysergic acid to a carbonyl, the configuration at this center may be changed as a result of heat- or base-catalyzed enolization (particularly in polar solvents) proceeding through a symmetric intermediate to afford the pharmacologically-inactive epimeric (+)-isolysergic acid and its derivatives. In the bioactive lysergic acid derivatives, the amide group is present in the 8-equatorial position, while in the inactive iso-forms, the group is axial. The lysergic acid derivatives commonly end in the suffix "-ine", while the their epimeric counterparts (the isolysergic acid derivatives) are assigned the suffix "inine."

Peptide Ergot Alkaloids (Ergopeptines)

The peptide alkaloids may be biosynthetically envisioned as tetrapeptides containing lysergic acid as the first member of the peptide chain. The other 3 classical amino acids are variable which accounts for the great diversity of the peptidic group of these alkaloids. Ergotamine and the other ergopeptines are composed of (+)-lysergic acid and a L-proline-containing complex tripeptide moiety. A unique structural feature not found in other naturally-occurring molecules is the cyclol part of the molecule, which results from the reaction of an α-hydroxyamino acid adjacent to lysergic acid with the carboxyl group of proline. Other commonly occurring amino acids present in the tripeptide portion of the ergopeptines include L-alanine, L-phenylalanine, L-valine, L-leucine, and L-isoleucine, as well as 2-aminobutyric acid. Ergotamine is the only naturally occurring ergopeptine to be used medicinally in the United States; however, useful semi-synthetic derivatives of peptide alkaloids include dihydroergotamine, bromocriptine (brominated ergocryptine), and dihydrogenated ergot alkaloids (ergoloid).

Ergot Alkaloid Biosynthesis [2,3,6,7,9,21-26]

The fundamental building blocks for the lysergic acid skeleton of the ergot alkaloids are the amino acid L-tryptophan and the isoprene dimethylallyl diphosphate, the latter deriving from 3R-mevalonic acid. Alkylation of L-tryptophan with dimethylallyldiphosphate affords 4-dimethylallyl-L-tryptophan which is N-methylated with S-adenosyl-L-methionine. Oxidative ring closure followed by decarboxylation, reduction, cyclization, oxidation, and allylic isomerization yields D-(+)-lysergic acid. The simple alkylamide derivatives of D-(+)-lysergic acid are readily formed, including ergine [D-(+)-lysergic acid amide] and ergonovine (ergometrine). The somewhat more complex peptides (ergopeptines) are formed via the sequential addition of activated amino acid residues (ATP-mediated) to thioester-bound lysergic acid, affording a linear lysergyl-tripeptide that is attached to the enzyme complex via covalent linkage as an enzyme complex. The cyclized tripeptide residue of ergotamine and other ergopeptines undergoes lactam formation that releases the product from the enzyme, followed by formation of a heimketal-like linkage.

Ergot Alkaloid Pharmacodynamics[11]

The pharmacological effects of the ergot alkaloids as a group tend to be complex and variable, with the net result of their actions being a sum of the effects of partial agonism or antagonism at adrenergic, dopaminergic, and serotonergic receptors. Variables relating to these effects are influenced by the agent, dosage, species, tissue, physiological, and endocrinological state, and experimental conditions.

Therapeutically Significant Lysergic Acid Amide Alkaloids
Ergonovine (Ergometrine, Ergobasine).[5,11,13,17,27,28]

Ergonovine was discovered in 4 different laboratories almost simultaneously, with 4 different names (ergometrine, ergotocine, ergosterine, and ergobasine) being assigned to the alkaloid. The names ergometrine and ergobasine have persisted in Europe, while ergonovine was adopted in the United States. The structure of ergonovine was elucidated in 1935 when it was shown that hydrolysis of the alkaloid afforded (+)-lysergic acid and (+)-2-aminopropanol. Ergonovine was introduced into world commerce in 1936 and first synthesized in 1938 via amidation of (+)-lysergic acid with (+)-2-aminopropanol. This represented the first synthesis of an ergot alkaloid. Ergonovine is a light-sensitive, water soluble compound that is commercially marketed as its water

soluble maleate salt. The compound is presently obtained from 3 different sources: isolation from field ergot as a minor byproduct, isolation from fermentation broth, and synthesis from (+)-lysergic acid and L-(+)-2-aminopropanol using variable coupling reagents.

Ergonovine is a selective and moderately potent tryptaminergic receptor antagonist in various smooth muscles, being only a partially agonistic or antagonistic at tryptaminergic receptors in the central nervous system. In blood vessels the alkaloid is only weakly antagonistic of dopaminergic receptors and partitally agonistic of α-adrenergic receptors. The most pronounced effect of ergonovine is one of direct stimulation of the uterine smooth musculature, resulting in increased muscular tone and an enhancement of the rate and force of rhythmical contractions. This stimulant effect seems to be most closely associated with agonist or partial agonist effects at 5-HT2 receptors. Food and Drug Administration (FDA) approved indications are for the treatment and prophylaxis of abortion complicated by delayed and/or excessive hemorrhage, and in the treatment and prophylaxis of postpartum hemorrhage due to uterine atony or subinvolution. The drug is administered after the expulsion of the placenta because prior administration may result in placental entrapment. Ergonovine maleate is typically administered intramuscularly or intravenously, with the intravenous route being reserved for emergency use. The drug is contraindicated for use in the induction of labor because it may jeopardize placental blood flow and fetal oxygen supply, and in cases of threatened spontaneous abortion, or in pregnancy (FDA Pregnancy Category X). Adverse reactions are generally gastrointestinal and are limited to nausea and vomiting (1%-10%). Ergonovine derivatives are substrates of CYP3A4 metabolism, and as such are contraindicated for concomitant use with compounds established as strong CYP3A4 inhibitors (including protease inhibitors, some macrolide antibiotics, quinolones, azole antifungals) because of the production of acute ergot toxicity. Finally, the drug has an off-label indication for use as a diagnositic test for Prinzmetal's angina (variant angina, vasospastic angina) in which it has been used successfully for noninvasive diagnosis of coronary vasospasm as a cause of chest pain. The drug is marketed as *Ergotrate* Eli Lilly and Co., Indianapolis, Ind) and is supplied as an intravenous solution (0.2 mg/mL) and oral tablets (0.2 mg).

Methylergonovine.[17,29]

Methylergonovine does not occur naturally in ergot, but was first introduced as a synthetic product for medical use in 1946. The drug is currently prepared via reaction of (+)-lysergic acid with L-(+)-aminobutanol, using different coupling reagents. Unlike its homologue ergonovine, methylergonovine has a low water solubility and as such is marketed as its water soluble maleate salt. It is used therapeutically much in the same manner as ergonovine, with the FDA approving the compound for the routine management of postpartum uterine atony and hemorrhage, after the delivery of the placenta. Adverse reactions and contraindications are similar to ergonovine. The drug is marketed as *Methergine* (Sandoz Pharmaceuticals, Princeton, NJ) and is administered via the same route and dosage as ergonovine.

Methysergide.[17,30,31]

Methysergide is another alkaloid-derivative that does not occur naturally in ergot, but was first introduced as a synthetic product into medical use in 1960. The drug is currently prepared via synthesis from (+)-lysergic acid or by methylation of ergonovine (ergometrine, ergobasine) and is marketed as its water soluble maleate salt. This semisynthetic compound is a potent 5-HT2 receptor antagonist that is postulated to stabilize neurotransmission in the trigeminovascular system to block the development of neurogenic inflammation. The FDA-labeled indication is for the prophylaxis of vascular headache, but therapy tends to be limited to those patients who suffer frequent and/or severe and uncontrollable vascular headaches that do not respond to other prophylactic measures. The compound is not indicated in the symptomatic treatment of acute headaches. The compound is known to produce retroperitoneal, pleuorpulmonary, and endocardial fibrosis on long-term administration in a small number of patients (0.02%). Methysergide is administered as an oral tablet (2 mg) and should not be taken continuously for longer than 6 months, with appropriate therapy requiring a 3-4 week treatment interruption, prior to resumption of therapy. The dosage of the medication needs to be gradually reduced over 2-3 weeks prior to discontinuation in order to avoid rebound headaches. Some gastrointestinal upset is a common adverse effect. Patients should be advised to discontinue the medication and consult their physician immediately in case of chest pain, cold feeling or bluish discoloration in the extremities, or pain in the calf. The drug is assigned as a FDA Pregnancy Category X compound. Methysergide has been marketed as *Sansert* (Novartis Pharmaceuticals, East Hanover, NJ).

Therapeutically Significant Peptide Alkaloids

Ergotamine.[2,5,11,13,17,28,31-33]

The isolation and naming of ergotamine by Stoll occurred in 1925 but the complete elucidation of structure was not achieved until 1951, with synthesis following some 10

years later. Current sources of ergotamine include the isolation from field ergot and fermentation broth, as well as synthesis via coupling of (+)-lysergic acid with the appropriate synthetic peptidic moiety. Ergotamine was introduced into world commerce in 1921, and is currently marketed as its water soluble tartrate salt.

Ergotamine is a partial agonist at various tryptaminergic receptors (including the serotonin receptor [5-HT2]) and at various α-adrenergic receptors in blood vessels and various smooth muscles. It is likely that the major activity of ergotamine and related alkaloids is one of agonism at the 5-HT1B/1D receptors, just as with the "triptan" antimigraine compounds. FDA-labeled indications for ergotamine tartrate are in the abortion or prevention of vascular headaches, such as migraine, migraine variant, cluster headache, and histaminic cephalalgia. The alkaloid is considered useful in the therapy of moderate to severe migraine attacks in which it acts to constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system. Both venous and arterial constriction occur at therapeutic dosage. Ergotamine is most effective when administered early in the migraine attack, preferably at the first indication of an impending event. Nausea and vomiting are the most common adverse effects of therapy due to stimulation of the medullary chemoreceptor trigger zone. Other common adverse effects include muscle weakness, fatigue, paresthesias, tightness in the chest, and diarrhea. Ergotamine tartrate is available as both oral (1 mg, with caffeine [100 mg]) and sublingual (2 mg) tablets (*Ergomar*), as well as rectal suppositories (2 mg, with caffeine [100 mg]). Caffeine is added to these preparations to enhance absorption and potentiate analgesia. Oral dosage is 2 mg at the onset of the attack, followed by 1-2 mg every 30 minutes as needed, with maximum dosage being 6 mg/day or 10 mg/week. Rectal dosage is 1-2 mg at onset, followed 1-2 mg every hour, as needed, with a maximum dosage of 4 mg/day or 10 mg/week. Dosage requirements to achieve an effective therapeutic subnauseating endpoint should be established and adhered to for future attacks. Prolonged administration or excessive dosage may result in severe peripheral vasoconstriction, ergotism, gangrene, or various fibrotic complications (cardiac valvular, retroperitoneal, pleuropulmonary). Ergotamine derivatives are contraindicated in patients with peripheral vascular disease, hepatic or renal disease, coronary artery disease, hypertension, sepsis, or pregnancy (FDA Pregnancy Category X). Ergotamine derivatives are substrates of CYP3A4 metabolism and as such are contraindicated for concomitant use with medications established as strong CYP3A4 inhibitors (protease inhibitors, some macrolide antibiotics, azole antifungals) because of the production of acute ergot toxicity.

Dihydroergotamine. [17,31,33,34]

Dihydroergotamine, which does not occur naturally in ergot, was first introduced as a semi-synthetic product in 1946. The drug is currently prepared either by hydrogenation of ergotamine isolated from field ergot/fermentation broth or via synthesis from dihydrolysergic acid and the appropriate synthetic tripeptide. Dihydroergotamine has a very low water solubility and is marketed for parenteral use as its water soluble mesylate (methanesulfonate) salt. FDA-labeled indications for the use of dihydroergotamine mesylate are for the acute treatment of the symptoms of migraine headache (w/wo aura) and for the acute treatment of cluster headache. The compound is poorly and erratically absorbed from the gastrointestinal tract and for this reason is available for intranasal and parenteral (intravenous, intramuscular, subcutaneous) administration. Following intranasal administration, the relative bioavailability is 30%-40%, with peak plasma concentrations reached in 30-60 minutes. The adverse effect profile resembles that of ergotamine, although dihydroergotamine is rarely associated with serious toxicities. Contraindications, precautions, and drug interactions are similar to those of ergotamine. Although parenteral administration was once mainly viewed as therapy reserved for inpatient or emergency department treatment for moderate to severe migraine, patients have been trained to administer the drug intramuscularly or subcutaneously. The administration of dihydroergotamine mesylate is not generally associated with the production of rebound headache, but dosage restrictions cited for ergotamine tartrate should be strictly observed to prevent this phenomenon. Dihydroergotamine mesylate is commonly available under the trade names of *D.H.E. 45* injection (Xcel Pharmaceuticals, San Diego, Calif) and *Migranal* nasal spray (Xcel Pharmaceuticals, San Diego, Calif).

Bromocriptine. [11,17,35-37]

Bromocriptine (2-bromo-α-ergocriptine) is not a naturally occurring ergot alkaloid, but is a semisynthetic derivative of the naturally occurring peptide alkaloid α-ergocriptine (α-ergocryptine, α-ergokriptine, α-ergokryptine) that has been isolated from field ergot/fermentation broth or prepared via synthesis from (+)-lysergic acid. Bromocriptine is prepared via the bromination of α-ergocriptine with different brominating agents and is marketed as its water soluble mesylate (methanesulfonate) salt. The compound was introduced onto the world market in 1975. Although bromocriptine exhibits only weakly antagonistic interactions with tryptaminergic and α-adrenergic receptors, the drug is a potent dopamine receptor agonist via activation of certain central dopamine D2 receptors. Bromocriptine is known to

stimulate both pre- and post-synaptic sites, promoting the release of dopamine and inhibiting dopamine uptake. The net effect is a decrease in the turnover rate of dopamine without significant changes in concentration.

FDA-labeled indications for bromocriptine are for the therapy of hyperprolactinemia and pituitary prolactinoma. Hyperprolactinemia is a state of persistent elevation of serum prolactin levels and may result in infertility and amenorrhea in females, and galactorrhea in both males and females. Prolactin is a hormone produced by the anterior pituitary, with increased serum levels of prolactin being associated with both benign secreting tumors of the gland (prolactinomas [prolactin-secreting adenomas]) and the use of centrally acting dopamine antagonists. Bromocriptine inhibits the release of prolactin by direct stimulation of postsynaptic dopamine receptors in the hypothalamus.

Other FDA-labeled indications for bromocriptine are in the therapy of acromegaly and as an adjunct to L-dopa therapy in patients with Parkinson's disease who are experiencing a deteriorating response to L-dopa or who are undergoing fluctuations in response to the drug. Other patients who may benefit from bromocriptine therapy include those with limited clinical response to L-dopa owing to an inability to tolerate higher doses. Dopamine agonist drug therapy is associated with an L-dopa-sparing effect and with a decrease in the frequency of off periods. Adverse effects of therapy may be dose-limiting, tending to occur more frequently at the onset of therapy, and being more likely with higher dosage or rapid escalation of dosage. Gastrointestinal upset (particularly nausea) is common and may also be accompanied by asymptomatic postural hypotension, sedation, light-headedness, and vivid dreams. Daytime sedation, confusion, and hallucinations are psychic effects that are often dose limiting. Ergot-like fibrotic complications are rare but may occur. Bromocriptine is marketed as a tablet (2.5 mg) and a capsule (5 mg) under the name of *Parlodel*. (Sandoz Pharmaceuticals, Princeton, NJ).

Closely related, orally administered synthetic drugs include pergolide mesylate (*Permax*) and cabergoline (*Dostinex*). Pergolide, a potent dopamine receptor agonist at both D1 and D2 receptor sites, has an FDA-labeled indication for use in the therapy of Parkinson's disease and non-FDA labeled indications for the therapy of hyperprolactinemia and Tourette's disorder (syndrome).[36-39] Cabergoline, a potent dopamine D2 receptor agonist with a low affinity for dopamine D1 receptors, is represented by an FDA labeled indication for use in the therapy of hyperprolactinemia, and non-FDA labeled indications for the therapy of Parkinson's disease, and suppression of puerperal lactation.[40]

Dihydrogenated Ergot Alkaloids.[2,5,9,13,17,20,41]

The peptide alkaloid ergotoxine was originally believed to be a single compound, but was subsequently shown to be a mixture of 3 peptide ergot alkaloids: ergocristine (30.0%-36.5%), ergocriptine (ergocryptine) (30.0%-36.5%), and ergocornine (30.0%-36.5%). Ergocristine was first isolated from Iberian ergot in 1937 and later found to be a constituent of ergotoxine in 1943. Both ergocryptine and ergocornine were first discovered as members of the ergotoxine complex in 1943. Later, ergocriptine was shown to be a mixture of 2 compounds α-ergocriptine and β-ergocriptine, in a ratio of 1.5:1.0 – 2.5-1.0. Each of the ergotoxine alkaloids contains a tripeptide ring, with 2 of the amino acids (valine and proline) being in common in all of the compounds, while the third differs. Dihydroergotoxine is prepared via isolation of the individual alkaloids or their mixtures from field ergot or fermentation broths, followed by catalytic hydrogenation and preparation of the methane sulfonate (mesylate) salts. Alternatively, dihydroergotoxine may be prepared via synthesis of the individual dihydroergotoxines by coupling dihydrolysergic acid with the corresponding synthetic peptidic portions, adjustment to the required ratio of individual components, and preparation of the mesylate salts.

Dihydroergotoxine mesylates, commonly known as ergoloid mesylates, has an FDA-labeled indication for use in the symptomatic therapy of age-related dementia, being employed in individuals over 60 years of age who manifest signs and symptoms of an idiopathic decline in mental capacity. Those who respond are thought to be ones suffering from some process related to aging or have some underlying condition of dementia, such as primary progressive dementia, Alzheimer's dementia, senile onset dementia, or multi-infarct dementia. The mechanism of action of dihydroergotoxine (ergoloid) mesylates in geriatric senility has not been determined. Although the drug has some α-blocking activity, it has no vasoconstrictor or oxytocic properties and controversy continues to exist as to whether there is any effect on cerebral arteriosclerosis, cerebrovascular insufficiency, or cerebral blood flow. Systemic bioavailability is higher with the liquid capsule than the tablet. Common adverse effects include gastrointestinal upset and headache. The drug is available in a liquid filled oral capsule (1 mg), oral tablet (1 mg), oral solution (1 mg/mL), and sublingual tablet (0.5 mg, 1 mg). Alleviation of symptoms may not be noticeable for 3-4 weeks and up to 6 months of therapy may be necessary to determine efficacy. The drug is a major substrate of CYP3A4, and drug interactions may be anticipated.

Hallucinogenic Ergot Alkaloid Derivatives

Lysergic acid diethylamide[2,10,11,42-46]

Lysergic acid diethylamide (German term:*lysergsauerediethylamid*) was first synthesized in 1938 in a screening of compounds for oxytocic activity and was the 25th semisynthetic ergot that Dr. Albert Hofmann of Sandoz AG in Basel, Switzerland, prepared by combining (+)-lysergic acid with different amines. The compound was tested in comparison with ergonovine and found to have less oxytocic activity and thus Sandoz pharmacologists ceased any further development of this particular formulation. According to company policy, LSD-25 should thereafter have been discounted and never resynthesized. However, on Friday, April 16, 1943, Dr. Hofmann, acting under a "peculiar presentiment" that the compound possessed as yet undiscovered properties, resynthesized the compound. He was interested in further investigating the analeptic activity of LSD-25 in comparison to nikethamide because of the partial structural similarities of the 2 compounds. Unknown to him, Hofmann accidentally ingested some of the product during the purification and crystallization of lysergic acid diethylamide tartrate, and was compelled to go home in midafternoon and lay down. He experienced a dazed and dream-like state, in which he sensed a distortion of time and was flooded with vivid, highly colored, kaleidoscopic images of extreme plasticity and unusual dimension. Several hours later he returned to normal and inherently understanding that these reactions had to be a result of something that he had come in contact with in the laboratory, was prompted to undertake a series of self-experiments ingesting the smallest quantity of an ergot alkaloid (0.25 mg) that at the time might be expected to produce a biological effect. On Monday, April 19, he separately ingested every product (in a dosage of 0.25 mg) with which he had worked the previous Friday. About 40 minutes after ingesting a solution of lysergic acid diethylamide tartrate the hallucinations and emotions that he had previously experienced returned. He spoke and wrote only with difficulty, and requested that his laboratory assistant accompany him home. As they rode their bicycles to his home (no automobiles used during WWII, except for designated individuals), Hoffmann's field of vision alternately wavered and became distorted, and he had the sensation of not being able to move from place to place, even though his assistant later confirmed that they had traveled rapidly. On arriving home, he asked his assistant to call for the family physician and also requested milk from his neighbors. He recovered in about 14 hours and his colleagues at Sandoz were astounded at his description of the event. A few of them ingested small doses of lysergic acid diethylamide (LSD) and confirmed Hofmann's description and experience. Since it is currently believed that marked behavioral changes occur in dosages of 25-50 nanograms (ng = 10^{-9} g), it can be estimated that Hofmann ingested roughly a 10,000-fold overdose of the hallucinogen. This unique man, who made such a staggering discovery in his seminal research with LSD, just recently reached his 100th birthday. Sandoz tried to find a therapeutic, commercial utility for LSD, even providing free samples and financial support to many investigators, but ultimately researchers observed that the experiences of a numerous variety of patients (psychiatric, alcoholic, cancer, and others) included as many adverse reactions ("bad trips") as beneficial ones.

LSD and related hallucinogens are known to interact with brain 5-HT receptors to produce agonist or partial antagonist effects on serotonin activity. This includes both the presynaptic 5-HT1A and 5-HT1B receptors, as well as the postsynaptic 5-HT2 receptors. Theoretically, LSD and other hallucinogens promote glutamate release in thalamocortical terminals, thus producing a dissociation between sensory relay centers and cortical output. It is not known whether the agonist property of these hallucinogens at 5-HT2C receptors contributes to behavioral alterations. LSD has also been demonstrated to interact with many other 5-HT receptors, including cloned receptors whose functions have not yet been determined. In any event, the precise mechanism by which hallucinogens exert their effects remains unsolved.

The onset of action of LSD is within 30-60 minutes, with effects peaking over 1-6 hours and dissipating in 8-12 hours. Acute toxicity includes gastrointestinal upset, chills, hyperglycemia, hypertension, mydriasis, tachycardia and panic, while chronic effects include flashbacks, and exacerbation of latent mental disorders, particularly schizophrenia. Overdosage most commonly results in "bad trips" that are characterized by intense anxiety, combativeness, confusion, and panic. Physical dependence and a withdrawal syndrome are absent and psychological dependence is low. Individuals experiencing a "bad trip" may usually be "talked down" or treated with a benzodiazepine. Because of its relatively high therapeutic index, no deaths have been directly attributed to LSD use alone.

LSD is sold on the illicit market in a variety of forms, including tablets, capsules, and a liquid form. Drops of solution are added to blotter paper, gelatin wraps, gelatin squares, candies, and sugar cubes. Stamped blotter paper containing common or popular cartoon characters is particularly common. When found in a solid form, the substance is a powder or crystal that is incorporated into capsules or tablets.

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