Multipotent and Poly-therapeutic Fungal Alkaloids of *Claviceps purpurea*

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Abstract

Claviceps are a group of phytopathogenic ascomycetes which includes around 50 known species. *Claviceps purpurea*, *Claviceps fusiformis*, *Claviceps paspali*, *Claviceps africana*, and *Claviceps lutea* are the most common and well-characterized fungi. Ergot alkaloids and other constituents derived from *Claviceps* are beneficial for various clinical applications in humans and animals. However, they also contain certain chemicals that are extremely addictive, abusive, and lethal. Ergot derivatives exhibit interesting pharmacokinetic and pharmacodynamic effects. Their pharmacodynamic actions are attributed to their agonistic, partial agonistic, and antagonistic effects on different receptors pertaining to the monoaminergic neurotransmitters. Due to their binding (with or without intrinsic effects) ability on the receptors, they induce numerous pharmacological effects which have potential medical values. Methysergide, ergotamine, dihydroergotamine, ergometrine (ergonovine), pergolide, ergoloid mesylates, and bromocriptine are the most popular ergot-based

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drugs used globally for treating numerous diseases. These drugs have been used to treat inflammatory-, infectious-, neurological-, cardiovascular-, gastrointestinal-, endocrinological-, sexual-, and urological-related pathologies. Hence, they are considered as a multipotent and poly-therapeutic fungus.

Keywords

Claviceps purpurea • Ergots • Medicinal value • Medicines derived from *Claviceps* • Neuroprotection

Contents

8.1 Introduction 231
8.2 Composition of *Claviceps* and Chemistry of the Ergots 231
8.3 General Pharmacokinetic Aspects Associated with *Claviceps* 235
8.4 Pharmacology of *Claviceps* 235
8.5 Drugs Derived from *Claviceps* 237
8.5.1 Methysergide 237
8.5.2 Ergotamine 238
8.5.3 Dihydroergotamine 239
8.5.4 Ergometrine (Ergonovine) 239
8.5.5 Pergolide 241
8.5.6 Ergoloid Mesylates (Hydergine) 242
8.5.7 Bromocriptine 243
8.5.8 Lysergic Acid Diethylamide (LSD) 246
8.6 Future Perspectives 248
8.7 Conclusions 248
References 249

Abbreviations

5-HT	Serotonin
AUC	Area under the curve
CNS	Central nervous system
D receptor	Dopamine receptor
DHE	Dihydroergotamine
FFA	Free fatty acid
GIT	Gastrointestinal tract
GPCRs	G protein-coupled receptors
HPPD	Hallucinogen persisting perception disorder
LSD	Lysergic acid diethylamide
MAO	Monoamine oxidase
MDMA	Methylenedioxymethamphetamine
PZQ	Praziquantel
Src	Proto-oncogene tyrosine-protein kinase
Trk	Tropomyosin receptor kinase

8.1 Introduction

The word *Claviceps* is derived from the Latin word "Clava" which means club and "-ceps" referred to as "headed" from the fungal shape (Dennis 1978). The genus *Claviceps* are a group of phytopathogenic ascomycetes of filamentous fungi, 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. *Claviceps* includes about 50 known species of which significant ones are *Claviceps purpurea* (parasitic on grasses and cereals), *Claviceps fusiformis* (on pearl millet, buffel grass), *Claviceps paspali* (on Dallis grass), *Claviceps africana* (on sorghum), and *Claviceps lutea* (on paspalum) (Bandyopadhyay et al. 1998). *Claviceps purpurea* is an ergot fungus that most commonly affects rye, wheat, and barley. It is the ergot stage of the fungus that harbors various compounds that have been useful as pharmaceutical drugs as well as mycotoxins that can be fatal when consumed. Mycotoxins are secondary metabolites of fungi that can induce pathologies and demise in plants, animals, and humans. Due to their wide pharmacodynamic effects, they have found use as drugs, medicine (antibiotics), and growth inducers and have been implicated as poison and used in chemical warfare agents. The proportion of the compounds produced varies within the species. The ergot family includes many alkaloids which contain the structural elements of the neurotransmitters serotonin, dopamine, and epinephrine. Therefore, ergot alkaloids can be recognized as ligands at a number of neurotransmitter receptors, as agonists or antagonists. They also act directly on the smooth muscles of the uterus causing contractions, thus their early use to induce abortion. The strongest biological effect of the ergots is intoxication, caused by specifically lysergic acid amides, one of which is the recreational (and illegal) drug, lysergic acid diethylamide (LSD). In this chapter, we have reviewed the studies on fungal alkaloids of *Claviceps purpurea having poly-therapeutic applications.*

8.2 Composition of *Claviceps* and Chemistry of the Ergots

The ergot sclerotium contains 30–40% of fatty oils and up to 2% of alkaloids (Komarova and Tolkachev 2001). It also contains free amino acids, ergosterin, choline, acetylcholine, ergothioneine, free aromatic and heterocyclic amines (tyramine, histamine), and alkylamines. The outer shell of sclerotium consists of anthraquinolinic acid derivatives (orange-red endocrinin, clavorubin and light yellow ergochromes, ergochrysins). Naturally growing *Claviceps purpurea* species differ both in the qualitative and quantitative composition of alkaloids. Hence these are identified based on a single alkaloid or certain group of alkaloids (ergotamine, ergotoxine, ergocristine) they produce (de Groot et al. 1998). Ergotoxine ethanosulfate was considered a pure substance and used as standard since its isolation. Later ergotoxine was shown to be a mixture of the three alkaloids ergocristine, ergocornine, and ergocryptine (Evans and Trease 1996). Six pairs of alkaloids predominate in the sclerotium and fall into the water-soluble ergometrine group or the water-insoluble

ergotamine and ergotoxine groups (Table 8.1). The ergot alkaloids possess high biological activity and a broad spectrum of pharmacological effects; hence they are of considerable importance to medicine. They affect adrenergic, serotoninergic, and dopaminergic neurotransmission. These compounds are now obtained both by methods of artificial parasitic cultivation on rye and by techniques using in vitro culture (Boichenko et al. 2001).

The naturally occurring ergot alkaloids are all indole-containing heterocycles biosynthesized from the amino acid L-tryptophan and the isoprene dimethylallyl diphosphate. Over 80 different ergot alkaloids have been isolated, mainly from various *Claviceps* species, as well as other fungi and plants. All of the ergots contain a tetracyclic ring system referred to as an ergoline which is a partially reduced indole [4,3-f,g] quinolone (Fig. 8.1). They also contain several centers of chirality, and all ergots have the R configuration at position 5 since this configuration is fixed by the biosynthetic precursor L-tryptophan. Depending on the structure of the ergoline D-ring and the nature of the substituent at C8, the ergots are subclassified as clavines, simple lysergic acid amide derivatives, and peptide ergot alkaloids (ergot peptides). These subclasses are biogenetically controlled, resulting from different biosynthetic pathways in the different organisms that form ergots.

The simple lysergic acid amides and peptide ergot alkaloids are amide derivatives of lysergic acid, with different types of amide functionality at C8; lysergic acid amide derivatives consist of simple secondary or tertiary alkyl amides, while the peptide ergots have a cyclic tripeptide amide (Fig. 8.1). The clavines typically contain a simple alkyl or alcohol group at position 8 instead of an amide and may have other functional groups present at position 9 or the indole ring. Generally, the ergoline ring is responsible for the base pharmacologic activity of the ergot alkaloids (serotonin antagonism, alpha or dopamine agonism, uterine contractility), while the differing ergoline ring substituents in the clavine, lysergic acid, and peptide ergot subclasses impart varying degrees of receptor specificity and agonist/antagonist activity. The only significant clavine derivative in therapeutic use today is the Parkinson drug pergolide. The primary ergot peptides of pharmacologic and

Table 8.1 Various ergot alkaloids and their formula

Group	Alkaloid	Formula
Ergometrine	Ergometrine	$C_{19}H_{22}O_2N_3$
	Ergotmetrinine	$C_{19}H_{22}O_2N_3$
	Ergotamine	$C_{33}H_{35}O_5N_5$
Ergotamine	Ergotaminine	$C_{33}H_{35}O_5N_5$
	Ergosine	$C_{30}H_{37}O_5N_5$
	Ergosinine	$C_{30}H_{37}O_5N_5$
	Ergocristine	$C_{35}H_{39}O_5N_5$
Ergotoxine	Ergocristinine	$C_{35}H_{39}O_5N_5$
	Ergocryptine	$C_{32}H_{41}O_5N_5$
	Ergocryptinine	$C_{32}H_{41}O_5N_5$
	Ergocornine	$C_{31}H_{39}O_5N_5$
	Ergocorninine	$C_{31}H_{39}O_5N_5$

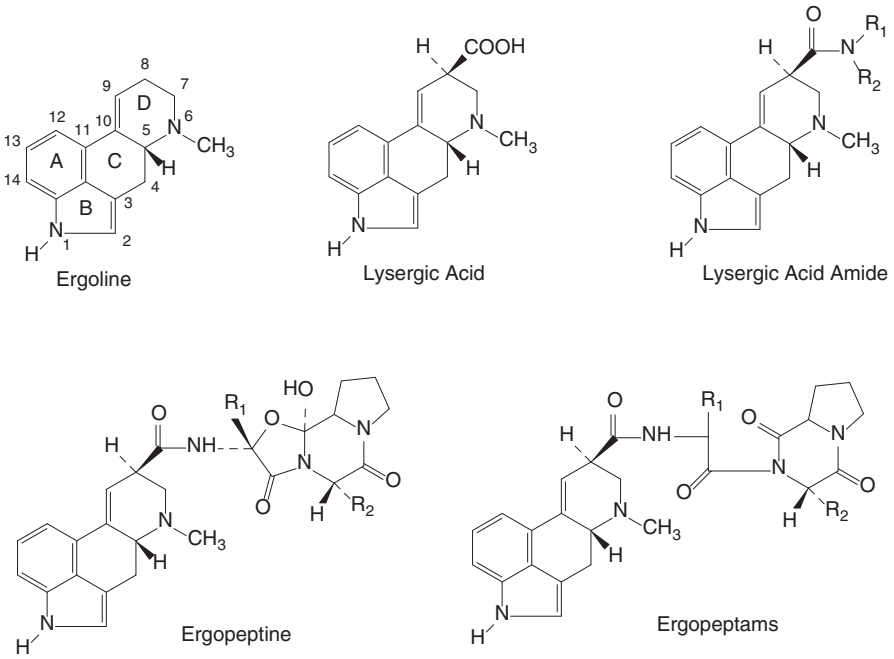

Fig. 8.1 Structures of the ergot derivatives

therapeutic interest are ergotamine, bromocriptine, and the ergoloid mesylates. LSD, methysergide, and ergonovine represent the principle lysergic acid derivatives of pharmacologic significance.

The ergot peptides traditionally are further subdivided into two classes, the ergopeptines and the ergopeptams (Fig. 8.1). The ergopeptides are the classic cyclic ergot alkaloids with an oxazolopyrrolopyrazine amide functionality derived from cyclization of three amino acids (cyclic tripeptide amides), and these are the most common naturally peptide ergot alkaloids. The ergopeptams, or E-seco-ergot alkaloids, have a diketopiperazine peptide amide substituent, also derived from amino acids. The ergopeptines and ergopeptams can be further subclassified based on their differing R1 and R2 substituents in the peptide fragment. For example, the ergopeptides are classified as valine derivatives when R2 is an isopropyl group (bromocriptine, ergoloid mesylates) or alanines (ergotamine) when R2 is a simple methyl group. The pharmacology of representative members of these series is discussed in the sections that follow. Ergopeptams typically are present in only small amounts and in certain ergot-producing organisms and are not therapeutically significant.

The lysergic acid and ergot peptides have two centers of chirality in their ergoline ring system at C5 and C8 (Fig. 8.1). Pharmacologically active ergots, the so-called left-handed isomers, typically have the 8R and 5R configuration. However, in the presence of a base (and even acid), the lysergic acid and ergot peptides readily undergo epimerization at C8 resulting in the formation of 8S and 5R diastereomers

(right-handed isomers). The epimerization occurs because the proton at C8 of these ergots is relatively acidic since it is on a carbon adjacent to both the amide carbonyl group and the double bond at C9–C10. These two functional groups electronically stabilize the negative charge of the carbanion that forms when the C8 proton is removed in base and thereby facilitate epimerization and loss of the R configuration. The resulting 8S epimers that form the lysergic acid ergots are referred to as isolysergic acid derivatives, and the 8S epimers of the ergopeptines are called ergopeptinines. These epimers typically have only weak or no pharmacological activity. Significant quantities of epimer may form during chemical extraction and processing and even during prolonged, improper storage. Interestingly no 8S isomers have been reported for ergopeptams, presumably because these ergots readily decompose into simpler derivatives in the presence of base or acid. Also, the chiral center at C5 of the lysergic acid and ergot peptides is chemically stable and does not undergo configurational inversion. Finally, the ergot peptides contain an additional four centers of asymmetry. These chiral centers are fixed by the biosynthetic process and do not epimerize. In most ergot alkaloids, the D-ring alkene bond is conjugated with the indole ring and therefore located at positions C9–C10 (Fig. 8.1). Reduction of this bond results in the formation of the corresponding dihydroergot derivative, such as reduction of ergotamine, and yields dihydroergotamine. Reduction of this alkene moiety also introduces a third chiral center into the ergoline nucleus. With respect to chemical reactivity, all of the ergot alkaloids are bases with the most basic atom being the nitrogen at position 6 of the ergoline ring. All other nitrogen atoms are relative nonbasic due to extensive aromatic conjugation as in the indole nitrogen at position 1 or the amide- and peptide-carbonyl conjugation in the case of the lysergic acid amides and ergot peptide side chains. As a result of this basicity, ergot salts can be prepared by reaction with mineral or organic acids. The other significant chemical reaction, the lysergic acid amides, and ergot peptides can undergo hydrolysis of any or all of the amide and peptide linkages. Complete hydrolysis of both lysergic acid amides and ergot peptides results in the formation of lysergic acid and the component amines or amino acids. It should be noted that the ergot peptide ergot alkaloids can also undergo decomposition reactions catalyzed by temperature, light, oxidizers, reducers, bases, and acids. As a result, these ergots can decompose under conditions of improper storage or during isolation and purification and even in the course of chemical analysis. Also, when administered to humans, the ergots are metabolized by several enzyme systems that can oxidize the portions of the ergoline ring or peptide side chain, as discussed in the sections that follow. Since their initial discovery, a large number of ergot derivatives have been synthesized by modifying either the ergoline ring system or amide-peptide portion of the ergot molecule. Most derivatives prepared to date have modified alkyl amides or tripeptide amide moieties or substitutions at positions 2, 5, or 13 of the ergoline ring system. Most noteworthy of these derivatives in terms of therapeutically useful agents have been the substitution of a bromine atom at position 2 of ergocriptine to yield 2-bromocriptine,an agent discussed in more detailed in the sections that follow.

8.3 General Pharmacokinetic Aspects Associated with *Claviceps*

With regard to the pharmacokinetic properties, ergot alkaloids are variably absorbed from the gastrointestinal tract (GIT). Bioavailability is of the order of 5% or less by the oral or rectal administration. The oral dose of ergotamine is about ten times larger than intramuscular dose. The rate of absorption and peak blood levels after oral administration can be improved by the administration of caffeine. The amine alkaloids are also absorbed from the rectum, buccal cavity, and aerosol inhaler. Absorption after intramuscular injection is slow but reliable. Bromocriptine is more completely absorbed from the GIT than ergotamine. More than 90% of the absorbed dose undergoes first-pass hepatic metabolism by the cytochrome P450 (CYP3A) system mainly by hydrolysis to lysergic acid and peptides, with the remainder of the dose which is hydrolyzed in the liver to inactive metabolites (Lam 2000; Kvernmo et al. 2008). Hence, patient on these drugs should avoid cytochrome P3A4 (CYP3A4) inhibitors, such as macrolide antibiotics (erythromycin, clarithromycin), antifungal drugs (ketoconazole, itraconazole, fluconazole, and clotrimazole), protease inhibitors (ritonavir, nelfinavir, indinavir, and saquinavir), antidepressants (nefazodone, fluoxetine, and fluvoxamine), cyclosporine, tacrolimus, and grapefruit juice (Wooltorton 2003). After intramuscular or intravenous administration, plasma concentrations decay in a bi-exponential fashion. The elimination half-life is 2–2.5 h, and clearance is about 0.68 L/h/kg. As noted above, metabolism occurs in the liver, and the primary route of excretion is the biliary.

8.4 Pharmacology of *Claviceps*

Ergot alkaloids act on several types of receptors (alpha-adrenergic, serotonin, and dopamine). They act as agonists, partial agonist, and antagonists at alpha-adrenergic receptors or serotonin (5-HT) receptors (Table 8.2). However, they only exhibit agonistic effect at the dopamine receptors. Naturally occurring alkaloids present in *Claviceps* exhibit powerful hallucinogenic effects. Lysergic acid diethylamide (LSD25) is a semisynthetic compound demonstrating hallucinogenic action and acts as peripheral (5 HT_2) receptor antagonist. Smooth muscles are the supporting tissue of blood vessels, stomach, intestine, and bladder. On vascular smooth muscles, it acts as vasoconstrictors and is due to partial agonistic effects at alpha-adrenergic receptors and 5-HT receptors. Vasoconstriction shows differential vascular sensitivity to ergot alkaloids of which most sensitive are cerebral arteriovenous anastomotic vessels. Anti-migraine specificity is mediated by neuronal or vascular serotonin receptors. Overdosage of ergotamine and related agents cause severe, long-lasting vasospasm which is not reversible by alpha-antagonists and serotonin antagonists. On uterine smooth muscle, ergot alkaloids have a stimulant effect which varies with hormonal status. The stimulant action involves serotonergic, alpha-adrenergic, and other effects. The uterine smooth muscle at term (during childbirth) is more sensitive than early pregnancy and far more so than the

Table 8.2 Actions of ergot derivatives

Ergot alkaloids	Alpha-adrenergic receptor	Dopamine receptor	Serotonin receptor (5 HT_2)	Uterine smooth muscle stimulation
Bromocriptine	Antagonist	Agonist	Antagonist	No effect
	Partial agonist			
Ergonovine	Agonist	Agonist	Partial agonist	Agonist
Ergotamine	Partial agonist	No effect	Partial agonist	Agonist
LSD	No effect	Agonist	Antagonist	Agonist
			Agonist (CNS)	
Methysergide	None	None	Partial agonist	None

nonpregnant organ. In small doses, ergot preparations can evoke rhythmic contractions and relaxation of the uterus. At higher doses, ergot preparations can induce a powerful and prolonged contraction. Ergometrine is more selective than other alkaloids and the agent of choice in obstetrics. Gastrointestinal smooth muscles show variable sensitivity causing nausea, vomiting, and diarrhea by activation of gastrointestinal serotonin receptors and central nervous system (CNS) chemoreceptor trigger zone emetic centers. There is no effect on bronchial smooth muscles. In the eye, ergotamine has alpha antagonist effect, producing miosis (constriction). Ergometrine has alpha agonist effect producing mydriasis (dilatation). Psoriasis is a chronic, common, and persistent dermatological pathology which significantly affects the life cycle of cells in the skin leading to increased cell growth on the surface of the skin. These dermal cells form thick, dry, and red patches, and silvery scales are itchy and painful. The various types of psoriasis are plaque psoriasis, nail psoriasis, scalp psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, and psoriatic arthritis. Malfunction of T cells has been an accepted etiology of psoriasis. Infection, obesity, stress, and smoking also can contribute to the etiopathology of psoriasis. The current therapeutic approaches are corticosteroids (topical), retinoids (topical), calcipotriene (Dovonex-vitamin D analog), anthralin, tacrolimus/pimecrolimus (calcineurin inhibitors), immunosuppressants (methotrexate, cyclosporine) salicylic acid, and moisturizers. The other nonpharmacological approaches are light therapy and avoiding alcohol and smoking. Bromocriptine possesses immunosuppressive properties, which may be related to its ability to lower circulating prolactin levels or to its direct suppressive effect on B and T cells (Morkawa et al. 1993; Morikawa et al. 1994). Due to the above effects, several studies reported the efficacy of bromocriptine in the treatment of psoriasis and psoriatic arthritis (Guilhou and Guilhou 1982; Eulry et al. 1995).

8.5 Drugs Derived from *Claviceps*

8.5.1 Methysergide

It is available as the maleate salt and is an ergot derivative and a congener of lysergic acid diethylamide, possessing nonselective serotonergic blocking activity (Johnson et al. 2003). Metabolites of methysergide also exhibit pharmacological activity. Methylergometrine (one of methysergide's metabolites) is responsible for methysergide's therapeutic effects regarding migraine treatment (Müller-Schweinitzer and Tapparelli 1986). Vascular headaches are a group of headaches that includes migraines. The vascular headaches involve abnormal function of the cerebral blood vessels or vascular system. The most common type of vascular headache is migraine which is characterized by severe pain on one or both sides of the head, nausea and/or vomiting, disturbed vision, and intolerance to light. Other kinds of vascular headaches include cluster headaches and headaches caused by a rise in blood pressure. Migraine is a complex disorder characterized by recurrent episodes of headache, most often unilateral and in some cases associated with visual or sensory symptoms—collectively known as an aura. The current therapy includes analgesics (acetaminophen, aspirin, ibuprofen, naproxen), caffeine, antidepressants, anti-nausea drugs (promethazine, chlorpromazine, prochlorperazine), and triptans (almotriptan, rizatriptan, sumatriptan). The other nonpharmacological approaches are acupuncture, biofeedback and cognitive behavioral therapy, spinal manipulation, diet changes, massage, meditation, neck stretching, and relaxation exercises. Methysergide's prophylactic action against migraine is via its nonselective action on 5-HT2c and 5-HT2b receptors on the vascular endothelium (Silberstein and Goadsby 2002; Johnson et al. 2003), while at the 5-HT_{1A} receptor it serves as a partial agonist. On systemic administration, it reaches maximum vasoconstrictor effect after 25 min and decreases within 50 min (Müller-Schweinitzer and Tapparelli 1986). By methysergide's action on the 5-HT2A receptor subgroup, it inhibits the release of histamine from mast cells (on 5-HT 2A receptor) (Young and Rozen 2005). 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. Methysergide is one of the most effective medications for the prevention of migraine, but not for the treatment of an acute attack (Joseph et al. 2003). Methysergide is also used to treat other recurrent throbbing headaches (Alliance 2008) and is also used in carcinoid syndrome to treat severe diarrhea and in the treatment of serotonin syndrome (Sporer 1995). It has a known side effect, retroperitoneal fibrosis which is severe, although uncommon. Other severe but uncommon side effects include pleural fibrosis and subendocardial fibrosis. In addition, there is an increased risk of left-sided cardiac valve dysfunction (Connolly et al. 1997; Joseph et al. 2003). The systemic availability of methysergide after oral administration is only 13%, due to a high degree of first-pass metabolism by N-1 demethylation to methylergometrine. After oral administration, the plasma concentrations of the metabolite are considerably higher than those of the parent drug, and

the area under the plasma concentration curve (AUC) for methylergometrine is more than ten times greater than for methysergide. Methylergometrine is a partial agonist/antagonist on multiple receptors such as serotonergic, dopaminergic, and alpha-adrenergic receptors.

8.5.2 Ergotamine

Ergotamine, marketed as the tartrate salt and often in combination with caffeine, is a peptide ergot derivative with nonselective serotonin 5-HT receptor agonistic activity and also has affinity for dopamine and noradrenaline receptors (Tfelt-Hansen et al. 2000; Villalon et al. 2003). The actions of ergot alkaloids at 5-$HT_{1B/1D}$ receptors likely mediate their acute antimigraine effects (Schaerlinger et al. 2003). The reduction product, dihydroergotamine (DHE), is also a α1-adrenoceptor antagonist. Ergotamine (Ergomar®) is available in oral and sublingual tablet formulation and rectal suppositories. With respect to pharmacokinetics, the oral absorption of ergotamine is 60–70 %, and concurrent administration of caffeine improves both the rate and extent of absorption (Bülow et al. 1986). Caffeine is thought to exert its rate-accelerating effect by increasing the water solubility of ergotamine, thereby assisting ergotamine absorption from a lipid phase (GI membrane) into an aqueous phase (blood) (Schmidt and Fanchamps 1974). However, ergotamine has low bioavailability as a result of substantial (greater than 90%) first-pass metabolism by the liver following oral administration, apparently involving CYP3A4. As a result, significant drug interactions can occur when ergotamine is administered with CYP3A4 inhibitors such as the macrolide antibiotics and protease inhibitor drugs. Ergotamine and its metabolites are excreted principally in the feces via biliary elimination.

The use of ergot alkaloids for a migraine should be restricted to patients having frequent, moderate migraines or infrequent, severe migraine attacks (Treves et al. 1998; Boureau et al. 2000). The drugs should be taken as soon as possible after the onset of a headache. The use of ergotamine has declined since the introduction of the triptans. Ergotamine has a more extensive adverse side effect profile (Young 1997; Morren and Galvez-Jimenez 2010) than the triptans, and clinical studies have shown that oral ergotamine plus caffeine is less effective than triptans for an acute migraine. Only the rectal forms of ergotamine are superior to rectal triptans. However, ergotamine may still be helpful for patients with status migrainous or those with frequent recurring headaches.

Side effects and contraindications include nausea and vomiting (occur in 10% of patients taking ergot alkaloids). They are contraindicated in patients with cardiovascular diseases. Due to teratogenic effects (pregnancy category X), it is contraindicated in pregnancy. Category X refers to studies where animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience. Risks involved in the use of the drug in pregnant women clearly outweigh potential benefits. It causes uterine contractions, fetal distress, gastrointestinal atresia, and miscarriage. These ergot alkaloids have a Black Box Warning for serious and/or

life-threatening peripheral ischemia which is associated with the coadministration of ergotamine with potent CYP3A4 inhibitors, including protease inhibitors and macrolide antibiotics. As CYP3A4 inhibition elevates the serum levels of ergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.

8.5.3 Dihydroergotamine

Dihydroergotamine (DHE) is synthesized by reducing an unsaturated bond in ergotamine. DHE is the currently used ergot preparation and marketed as the mesylate salt. An orally inhaled formulation of DHE delivered to the systemic circulation will be available in the near future (Aurora et al. 2011). DHE, a semisynthetic product, 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. The structural differences between ergotamine and DHE are small but significant. DHE has a hydrogen atom projecting below the plane of the ring at C(10) in the same direction as the proton on N(6), whereas ergotamine has none (Berde and Schild 1978). This modification results in a changed pharmacologic profile with dihydroergotamine exhibiting greater alpha-adrenergic antagonist activity and much less potent arterial vasoconstriction and emetic potential. Both ergotamine and DHE are 5-HT1A, 5-HT1B, 5-HT1D, and 5-HT1F receptor agonists. FDA-labeled indications for the use of dihydroergotamine mesylate are for the acute treatment of the symptoms of a migraine headache (w/wo aura) and for the acute treatment of a cluster headache. Following intranasal administration, the relative bioavailability is 30–40%, with peak plasma concentrations reached in 30–60 min. Dihydroergotamine is administered as a nasal spray form (Migranal®) or by injection. Four metabolites of dihydroergotamine have been identified in human plasma following oral administration. The major metabolite, 8′-β-hydroxy-dihydroergotamine, exhibits affinity equivalent to its parent for adrenergic and 5-HT receptors and demonstrates equivalent potency in several venoconstrictor activity models, in vivo, and in vitro. The other metabolites (i.e., dihydrolysergic acid, dihydrolysergic amide, and a metabolite formed by the oxidative opening of the proline ring) are of minor importance. Following nasal administration, total metabolites represent only 20–30% of plasma AUC. The systemic clearance of dihydroergotamine mesylate following IV and IM administration is 1.5 L/min. Quantitative pharmacokinetic characterization of the four metabolites has not been performed.

8.5.4 Ergometrine (Ergonovine)

Ergometrine is an amine ergot alkaloid included in World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system. Ergometrine has effects on uterine and vascular smooth muscle.

Usual therapeutic doses of ergometrine produce intense contractions of the uterus followed by periods of relaxation. The amplitude and frequency of uterine contractions increase which in turn impedes uterine blood flow thereby promoting hemostasis. With larger doses, basal uterine tone is elevated, and these relaxation periods will be decreased. Ergometrine also increases contractions of the cervix. The sensitivity of the uterus to the oxytocic effect is much greater toward the end of the pregnancy. Oxytocin is secreted by the posterior lobe of the pituitary gland. It is a neuropeptide that was primarily known for its role in the birth process and also in nursing. Oxytocin induces uterine contractions during labor and helps shrink the uterus after delivery. Oxytocin also has an antianxiety (anxiolytic) effect and may increase romantic attachment and empathy. It has therapeutic effects in patients with autistic spectrum disorders and appears to play a role in protecting the intestine from damage, with potential for use in the treatment of irritable bowel disease. These oxytocic actions of ergometrine are greater than its vascular effects (Gilman and Gilman 1985). Vasoconstriction is predominant in capacitance vessels thereby increasing central venous pressure and blood pressure. At high doses, ergometrine causes vasoconstriction of coronary arteries (Kimball et al. 1989). Like other ergot alkaloids, ergometrine produces arterial vasoconstriction by stimulation of α-adrenergic and serotonin receptors. The drug has only slight α-adrenergic blocking activity, and its vasoconstrictor effects are less than those of ergotamine (de Groot et al. 1998). In CNS, ergometrine is a partial agonist and partial antagonist at some serotonin and dopamine receptors. Ergometrine also possesses weak dopaminergic antagonist actions in certain blood vessels and partial agonist action at serotonin receptors in umbilical and placental blood vessels (Gilman and Gilman 1985).

Pharmacokinetics: Uterine contractions are usually initiated within 5–15 min following oral administration, within 2–3 min after IM injection, and 1 min following IV injection.
Half-life: 1–5 min (initial phase) and 0.5–2 h (terminal phase).
Duration in uterine effects: 3 h (IM) and 45 min (IV).

With regard to indications, as a prophylactic drug, ergometrine is administered after the delivery of the placenta for the purpose of contracting the uterus in order to prevent postpartum and postabortion hemorrhage due to uterine atony (Goodman et al. 2001). As a treatment, ergometrine is administered after the delivery of the placenta to promote involution of the uterus in order to treat postpartum and postabortion hemorrhage (Goodman et al. 2001); 0.2 mg IM is administered and may be repeated in 2–4 h, not to exceed five doses total. In diagnosing and testing, ergometrine maleate or methylergometrine maleate has been used as a provocation test for the diagnosis of variant angina (Prinzmetal's angina). Ergometrine maleate was used in the past to diagnose esophageal spasm (Schwartz and Kaufmann 1984). The major contraindications are previous hypersensitivity or idiosyncratic reactions to ergometrine, eclampsia or preeclampsia, severe or persistent sepsis, peripheral vascular disease, or heart disease, and in patients with hypertension or a history of hypertension, Raynaud's phenomenon, impaired hepatic, or renal function exists.

Ergometrine is rapidly absorbed after oral or IM administration. Following oral administration, bioavailability is highly variable but averages about 60%. Due to its lipophilic nature, the drug is rapidly distributed to tissues and into breast milk. It is metabolized by the liver by CYP3A4, but the metabolites have not been characterized. As a result, drug interactions are possible when ergometrine is coadministered with drugs that are inhibitors of CYP3A4, increasing the risk for vasospasm, cerebral ischemia, and/or ischemia of the extremities. This drug is excreted principally in feces and bile.

8.5.5 Pergolide

Pergolide is a semisynthetic clavine ergot derivative marketed as the mesylate salt and is predominantly D2 receptor agonist, with some weak actions at the Dl and D3 (Perachon et al. 1999) as well as on serotonin receptors. It possesses intrinsic activity at the dopamine D1 receptor which offers an additional advantage compared to other antiparkinson dopamine agonists (McClure et al. 2010). Pergolide also promotes the striatal expression of the dopamine D3 receptor (Perachon et al. 1999) and exerts actions on many subtypes of 5-hydroxytrptamine (5-HT) 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, and 5-HT2C receptors and α-adrenoceptors (Ruffolo, Jr. et al. 1987; Deleu et al. 2002).

Pharmacokinetics: It is well absorbed orally and has plasma half-life in the range of 3–7 h (Gilman and Hardman 1996). The drug undergoes extensive hepatic first-pass metabolism by oxidative N-dealkylation and sulfur oxidation and is approximately 90% bound to plasma proteins. It differs from bromocriptine in that it has a longer half-life, is substantially more potent, and has Dl agonist properties (Gilman and Hardman 1996).

Indications and clinical uses: In Parkinson's disease, levodopa has been considered as the sole drug in the treatment of its symptoms, but because of unwanted adverse effects such as long-term motor fluctuation and dyskinesia, the current guidelines suggest delaying of initiation of levodopa treatment and advocating an early use of dopamine agonists which offer several theoretical advantages over levodopa because of the underlying reasons. First, dopamine agonists act directly on dopamine receptors and do not require metabolic conversion to an active product in order to exert their pharmacologic effect. Hence they act independently of the degenerating dopaminergic neurons, and through this way the increased dopamine metabolism that would result from levodopa administration which may damage the nigrostriatal system through free radical generation is prevented. Nevertheless, dopamine agonists do not undergo oxidative metabolism and do not generate free radicals or induce oxidative stress. In addition, they have the potential to stimulate the presynaptic autoreceptors of dopamine and may, therefore, reduce endogenous dopamine turnover which is enhanced by levodopa and has been proven to be potentially toxic. Second, in contrast to levodopa, circulating plasma amino acids do not compete with dopamine agonists for absorption and transport into the brain. Third, dopamine agonists have a longer half-life than immediate-release and

controlled-release formulations of levodopa, and individual doses, therefore, have the potential to provide more sustained stimulation of striatal dopamine receptors. Finally, there is mounting evidence suggesting that they may have neuroprotective effects (Marsden et al. 1982; Lange 1998; Olanow et al. 2001; Deleu et al. 2002). Other uses of pergolide include treatment of depression in Parkinson's disease (Rektorová et al. 2003) and restless leg syndrome (Earley et al. 1998; Bassetti et al. 2002) and in the symptomatic treatment of Tourette syndrome (Eric et al. 2001; Gilbert et al. 2003) and prolactinoma.

Side effects: The drug is in decreasing use, as it was reported in 2003 to be associated with a form of heart disease called cardiac fibrosis (Breitenstein et al. 2006) (Research; Breitenstein et al. 2006). Pergolide is not currently available in the United States for human use, due to its action at the 5-HT2B serotonin receptors of cardiac myocytes, causing proliferative valve disease by the same mechanism as ergotamine, methysergide, fenfluramine, and other serotonin 5-HT2B agonists (Jähnichen et al. 2007). Pergolide can rarely cause Raynaud's phenomenon. In March 2007, pergolide was withdrawn from the US market for human use, due to serious valvular damage that was shown in two independent studies (Zadikoff et al. 2006; Schade et al. 2007). Pergolide has also been shown to impair associative learning (Markham and Benfield 1997).

8.5.6 Ergoloid Mesylates (Hydergine)

Ergoloid mesylates (Hydergine) contain derivatives of three naturally occurring ergot alkaloids – ergocristine (30.0–36.5%), ergocriptine (ergocryptine) (30.0–36.5%), and ergocornine (30.0–36.5%). Ergoloid mesylates have therapeutic efficacy in the treatment of dementia (Alzheimer's disease) and age-related cognitive impairment as well as to aid in recovery after stroke. However, the mechanism of action in dementia is unknown. It stimulates dopaminergic and serotonergic receptors and blocks alpha-adrenoreceptors (Markstein 1985). Modulation of synaptic neurotransmission rather than solely increasing blood flow has been proposed (Rowell and Larson 1999). Also, aging is associated with increase in monoamine oxidase (MAO) levels resulting in decreased availability of catecholamines in the synaptic cleft (Kennedy and Tanenbaum 2000). It possesses antioxidant and vasodilator effects in the vasculature of the brain. Although current lines of evidence suggest that cerebrovascular factors can worsen or accelerate the course of Alzheimer's disease, there is no convincing evidence that it actually increases the effective flow of blood to diseased areas of the human brain or that they have any clinical efficacy in dementia. Hence they are no longer used or recommended drug. It has peripheral alpha-blocking activity and also depresses CNS vasomotor nerve activity resulting in a slight decrease in blood pressure and hypertension.

8.5.7 Bromocriptine

Bromocriptine mesylate is a semisynthetic ergot alkaloid with potent dopamine receptor agonist activity. Dopamine receptors are a class of G protein-coupled receptors implicated in many neurological processes, including motivation, pleasure, cognition, memory, learning, and fine motor control, as well as modulation of neuroendocrine signaling. Bromocriptine mesylate inhibits prolactin secretion and lowers blood levels of growth hormone in acromegaly. Quick-release formulation of bromocriptine (Cycloset) is thought to act on circadian neuronal activities within the hypothalamus to reset abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in patients with insulin resistance. With regard to the pharmacokinetic aspect, absorption is 28 % from GI tract with bioavailability of 28% for Parlodel and 65–95% for Cycloset. Bromocriptine binds to albumin (90–96%) with the volume of distribution of 61 L. It is metabolized completely in the liver, with a half-life elimination of 4–4.5 h (initial phase) and 8–20 h (terminal phase). Excretion is mainly by feces (85%) and via biliary elimination.

Indications of Bromocriptine: It is used to treat hyperprolactinemia and prolactinomas (Parlodel). Secretion of the anterior pituitary hormone prolactin is inhibited without affecting other pituitary hormones. It is a potent suppressor of lactation. Since dopamine is an inhibitor of prolactin release, drugs increasing dopaminergic neurotransmission such as bromocriptine are useful and widely used in the treatment of these endocrine disorders (McMurray et al. 1995). About 80 % of hyperprolactinemic women treated with bromocriptine resume their normal menstrual cycles, and pregnancy rates may be as high as 70%. It induces menses in amenorrheic women and maintains normal levels of serum prolactin possibly via the release of luteinizing hormone (Cottigham 2004). Bromocriptine is the drug of choice for the treatment of hyperprolactinemia regardless of the etiology. In prolactin-secreting tumors, it reduces prolactin level and causes a reduction in tumor size as long as therapy continues; however tumor size rebounds upon cessation of treatment. The dose of bromocriptine used for hyperprolactinemia, amenorrhea, and male or female infertility is initially 1.25–2.5 mg once per day and then increased to a maintenance dose of 2.5 mg two or three times daily (Delgrange et al. 1998). Bromocriptine is used as a conservative treatment of pituitary micro- or macroprolactinomas, in presurgical reduction of tumor size to facilitate resection, and in postsurgical inhibition of persistent hyperprolactinemia. Bromocriptine is used to suppress or prevent puerperal lactation and prevent lactation following abortion in puerperal breast engorgement and incipient puerperal mastitis (Eftekhari 2004). It is also used in treating benign breast disease and controlling premenstrual symptoms (Delgrange et al. 1998). Acromegaly is caused by excessive secretion of growth hormone after the growth plate cartilage fuses in adulthood. Gigantism refers to abnormally high linear growth due to excessive growth hormone secretion while the epiphyseal growth plates are open during childhood. Somatotroph adenomas (growth hormone-producing adenomas) account for over 80% of the cases of acromegaly for which the treatment of choice is irradiation or surgical removal of the tumor. Drug therapy

is indicated for patients not cured by surgery and those with recurring problems. Growth hormone secretion by adenomas can be suppressed by bromocriptine. The effect of bromocriptine on growth hormone secretion is paradoxical, as it can actually increase growth hormone secretion in normal pituitary. It can reduce serum growth hormone by 50% or more in approximately half of patients treated, although not usually to normal levels. Since the effects of external pituitary radiation may not become maximal for several years, adjunctive therapy with bromocriptine mesylate offers potential benefit before the effects of irradiation are manifested. The dose in acromegalic patients is 1.25 mg two or three times daily, gradually increasing to 10–20 mg daily depending on clinical response and adverse reactions (Cassar et al. 1976).

Most patients with Parkinson's disease are treated with levodopa or with dopamine agonists. Bromocriptine has been used in previously untreated patients with Parkinson's disease to prolong levodopa treatment and delay its complications (Yamashita et al. 1995). While some neurologists use bromocriptine early in the treatment of Parkinsonism in an attempt to delay therapy with levodopa, others reserve it for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. Bromocriptine is sometimes useful in reducing "off" periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease (Parfitt 1999). Bromocriptine mesylate tablets or capsules are indicated for the treatment of the signs and symptoms of idiopathic or postencephalitic Parkinson's disease. As adjunctive treatment to levodopa (alone or with a peripheral decarboxylase inhibitor), bromocriptine mesylate therapy may provide additional therapeutic benefits in those patients who are currently maintained on optimal dosages of levodopa, those who are beginning to deteriorate (develop tolerance) to levodopa therapy, and those who are experiencing end of dose failure on levodopa therapy. Bromocriptine mesylate therapy may permit a reduction of the maintenance dose of levodopa and thus may ameliorate the occurrence and/or severity of adverse reactions associated with long-term levodopa therapy such as abnormal involuntary movements (e.g., dyskinesias) and the marked swings in motor function (on-off phenomenon). Continued efficacy of bromocriptine mesylate therapy during treatment of more than 2 years has not been established. The basic principle of bromocriptine mesylate therapy is to initiate treatment at a low dosage and, on an individual basis, increase the daily dosage slowly until a maximum therapeutic response is achieved. The dosage of levodopa during this introductory period should be maintained, if possible. The initial dose of bromocriptine mesylate is 1.25 mg twice daily with meals. Assessments are advised at 2-week intervals during dosage titration to ensure that the lowest dosage producing an optimal therapeutic response is not exceeded. If necessary, the dosage may be increased every 14–28 days by 2.5 mg/day with meals. The safety of bromocriptine mesylate has not been demonstrated in dosages exceeding 100 mg/day (Willis 2005).

Psoriasis is a complex, chronic, multifactorial, inflammatory disease that involves hyperproliferation of the keratinocytes in the epidermis, with an increase in the epidermal cell turnover rate. Environmental, genetic, and immunologic factors appear to play a role. The disease most commonly manifests on the skin of the

elbows, knees, scalp, lumbosacral areas, intergluteal clefts, and glans penis. In up to 30% of patients, the joints are also affected. Bromocriptine has also been used in the treatment of psoriasis. Increase in the severity and extent of psoriasis correlates with the development of a prolactin-secretory pituitary gland microadenoma. Prolactin may play a role in the pathogenesis of psoriasis because it plays an important part in the immune reactions and exerts a proliferative effect on human keratinocytes. The degree of elevation of prolactin is related to the severity of psoriasis. However, in all patients, administration of bromocriptine as a treatment of prolactinoma was associated with a better therapeutic response in psoriatic cutaneous lesions. Bromocriptine can be useful in the treatment of different autoimmune diseases. It has been used in the treatment of psoriasis vulgaris and psoriatic arthritis with a marked improvement in the lesions (Regaña and Umbert Millet 2000).

Bromocriptine is a sympatholytic D2-dopamine agonist that has been FDA approved for the treatment of type 2 diabetes. Based on animal and human studies, timed bromocriptine administration within 2 h of awakening is believed to augment low hypothalamic dopamine levels and inhibit excessive sympathetic tone within the central nervous system (CNS), resulting in a reduction in postprandial plasma glucose levels due to enhanced suppression of hepatic glucose production. Bromocriptine has not been shown to augment insulin secretion or enhance insulin sensitivity in peripheral tissues. However, the addition of bromocriptine to poorly controlled type 2 diabetic patients treated with diet alone, metformin, sulfonylureas, or thiazolidinediones produces a 0.5–0.7% decrement in HbA_{1c}. Bromocriptine also reduces fasting and post-meal plasma free fatty acid (FFA) and triglyceride levels.

Autonomic dysfunction after traumatic brain injury is usually associated with hypertension. The hypertension encountered in traumatic brain injury is described as being part of a hyperadrenergic state because it is associated with elevation of urine and blood catecholamine levels. Bromocriptine can cause hypotension, so it is used in the management of labile hypertension associated with autonomic dysfunction. Treatment is started with a low dose (0.025 mg/kg twice daily) and gradually increased to 0.05 mg/kg t.d.s. as required to treat the autonomic dysfunction. So, bromocriptine is an effective alternative treatment for the episodes of autonomic dysfunction due to severe traumatic brain injury or due to other causes (Russo and O'Flaherty 2000). Bromocriptine is also used to reduce the intensity of psychiatric symptoms associated with cocaine withdrawal (Cottigham 2004). Recently, it has been reported that dopamine receptors are effective targets for nerve regeneration. Höglinger et al. (2004) reported that dopamine D_2 receptor agonists, including bromocriptine, stimulate precursor cells to proliferate. Moreover, it increased the number of $BrdU^+$ cells and restored the nigrostriatal pathway in a model of Parkinson's disease (Van Kampen and Eckman 2006). These reports suggest that dopamine agonists increases neurogenesis, neuroprogenitor proliferation, and neuritic outgrowth. However, amine ergot alkaloids, including ergometrine and methylergometrine, did not induce neurite outgrowth. These results indicate that the structure of amino acid ergot alkaloids is important for the effect of bromocriptine. The primary site of action of bromocriptine remains to be identified. It is possible that bromocriptine-induced neurite outgrowth via activation of tropomyosin receptor kinase A (TrkA).

Moreover, K-252a, known as a Trk inhibitor, did not inhibit bromocriptine-induced neurite outgrowth. These results suggest that bromocriptine could not directly activate the signaling pathway mediated by TrkA. Recent reports indicate that G protein-coupled receptors, such as the purine $P2Y_2$receptor, adenosine A_{2A} receptor, and adrenaline α_2 receptor, induce neurite outgrowth via the activation of proto-oncogene tyrosine-protein kinase (Src) (Arthur et al. 2006; Karkoulias et al. 2006; Nakata 2007). Thus, amino acid ergot alkaloids, including bromocriptine, might activate Src via G protein-coupled receptors. However, talipexole and pramipexole do not induce neurite outgrowth, and clonidine, adrenaline α_2 receptor agonist, also did not. These results suggest that the effect of adrenaline α_2 receptor agonist is not sufficient for neurite outgrowth. Bromocriptine stimulates antioxidant mechanisms in the brain and acts as a free radical scavenger in addition to its action at dopamine receptors, thus indicating its strength as a valuable neuroprotectant (Muralikrishnan and Mohanakumar 1998).

Bromocriptine is used in bodybuilding though it is not an FDA-approved indication. It acts by prolactin inhibition, similar to that of progestin-based compounds (trenbolone and nandrolone decanoate). They increase prolactin levels which tend to increase the incidence of prolactin-based gynecomastia. Bodybuilding involves restricted calorie intake, which leads to decrease in leptin levels, and the body responds by holding onto nutrient stores. Bromocriptine helps normalize the slowing metabolism during this time and helps maintain normal leptin stimulation. This phenomenon is connected to its dopamine effects. Another off-label use of bromocriptine is in the treatment of the neuroleptic malignant syndrome. Bromocriptine is marketed as the mesylate salt which has relatively high bioavailability (65–95%) due to its lipophilic nature. The drug is highly bound to plasma albumin (90–95%) and highly distributed (volume of distribution 60 L). Bromocriptine undergoes extensive metabolism primarily by hydrolysis of the amide bond to produce lysergic acid and a peptide fragment, both of which are inactive and nontoxic. Bromocriptine is also metabolized by CYP3A4 and excreted primarily in the feces via biliary secretion (>80%). Because of this clearance profile, patients with a significant hepatic impairment may have elevated plasma levels of the active drug when bromocriptine is administered in standard doses. The half-life of the drug in patients with normal hepatic function is approximately 5–6 h.

8.5.8 Lysergic Acid Diethylamide (LSD)

It is a psychedelic drug also known as entactogen (to touch within) which is one of the most potent psychoactive compounds and was first synthesized by Albert Hofmann in Switzerland, in 1938 from ergotamine, while researching the medical effects of ergot-derived synthetic molecules (Wu et al. 2012). However, in 1943, Hofmann unintentionally ingested the substance and experienced stimulatory effects in the CNS, and hence the hallucinogenic properties of LSD were discovered (Sanders-Bush and Hazelwood 2011). Currently, LSD is known for its use as a "club drug," together with 3,4 methylenedioxymethamphetamine (MDMA). LSD

induces intense spiritual experiences, during which users may feel they have come into contact with a greater spiritual or cosmic order. Users sometimes report out of body experiences. LSD interacts with brain 5-HT receptors to produce agonist or partial antagonist effects on serotonin activity (Halberstadt and Geyer 2011). Activation of 5-HT2A also leads to increased cortical glutamate levels probably mediated by thalamic afferents thus producing a dissociation between sensory relay centers and cortical output (Marona-Lewicka et al. 2005). LSD also stimulates dopamine D2 receptors, leading to a biphasic pharmacologic pattern of early serotonin like effects (15–30 min after administration) and late mediated dopamine-like effects (60–90 min after administration). The onset of action of LSD is within 30–60 min, with effects peaking over 1–6 h and dissipating in 8–12 h. LSD is rapidly metabolized in the liver by N-demethylation, N-deethylation, and aromatic hydroxylation, and metabolites are excreted in the urine. The elimination half-life of LSD is 3–5 h. Physical dependence and withdrawal syndromes are absent, and psychological dependence is low. However, users develop a high degree of tachyphylaxis due to downregulation of 5-HT2A receptors. Long-term effects of chronic use can result in persistent psychosis and hallucinogen-persisting perception disorder (HPPD), so-called flashbacks (Abraham 1983). LSD remains one of the most potent mood-altering and perception-altering drugs because of its relatively high effect, and no deaths have been directly attributed to LSD use alone (Mello and Mendelson 2012). LSD is not considered an addictive drug because it does not produce compulsive drug-seeking behavior. However, LSD does produce a physiologic tolerance, requiring subsequently increased doses to achieve the same effect. Acute toxicity includes gastrointestinal upset, chills, hyperglycemia, hypertension, mydriasis, tachycardia, and panic attacks. The chronic effects include flashbacks and exacerbation of latent mental disorders, particularly schizophreniform psychosis and derangements in memory function, problem-solving, and abstract thinking. Overdosage most commonly results in "bad trips" that are characterized by intense anxiety, confusion, and panic. LSD is sold on the illicit market in a variety of forms, including tablets, capsules, and a liquid form. Drops of the solution are added to blotter paper, gelatin wraps, gelatin squares, candies, and sugar cubes. Stamped blotter paper containing 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. The drug can be detected by radioimmunoassay; levels from 1.5 to 5.5 ng/mL may be found within 24 h after the patient has taken a 300-mcg dose of LSD. However, high-performance liquid chromatography or gas chromatography is required for confirmation. LSD levels in the urine do not correlate with severity of symptoms (Berg et al. 2013). Hope was placed in these substances for new treatments for psychiatric conditions and discoveries that would "unlock the mysteries" of the mind. The research of LSD faded because the clinical promises failed to be realized while the illicit use of the drug grew exponentially. Today, LSD and other hallucinogens are once again being evaluated for specific purposes, such as for treatment of a cluster headache and as tools in therapy for working with those suffering from anxiety provoking end-of-life issues and for posttraumatic stress disorder.

Following oral administration, plasma lysergic acid diethylamide concentrations are detectable for up to 12 h. Maximum concentrations of lysergic acid diethylamide are reached within 1.5 h after administration and then decrease following first-order kinetics with a half-life of 3–4 h up to 12 h and slower elimination thereafter with a terminal half-life of over 9 h. Only a small fraction (1%) of the oral dose of LSD is eliminated in urine as lysergic acid diethylamide, while about 15% is eliminated as 2-oxo-3-hydroxy-lysergic acid diethylamide within 24 h. The acute subjective and sympathomimetic responses to LSD last up to 12 h and closely correlate with plasma concentrations over time.

8.6 Future Perspectives

Ergot alkaloids as treatment for schistosomiasis: The parasitic infection schistosomiasis is clinically treated using a single drug, praziquantel (PZQ). However, the molecular basis of action of this clinical agent is poorly understood, hence exploiting the predictive phenology between free-living planarian regenerative screens and parasitic neuromuscular physiology to reveal a broad efficacy of ergot alkaloids in phenocopying the action of PZQ. Ergot alkaloids with efficacy in regenerative assays were also found to modulate the contractility of schistosomules. Overall, these data highlight a possible therapeutic potential of ergot alkaloids as antischistosomals and the action of PZQ as an ergomimetic. Indeed, ergot alkaloids have a well appreciated ability to modulate smooth muscle contraction based on their bioaminergic mimicry, a property that underpins several of their applications in the clinic. This ergomimetic quality to PZQ action provide impetus for considering ergot alkaloids as potential drug leads for manipulating bioaminergic G protein-coupled receptors (GPCRs) to provide next-generation antischistosomals (Ribeiro et al. 2012). In conclusion, the ergot alkaloid scaffold merits further exploration by medicinal chemistry to identify novel chemotherapeutics with efficacy against parasite muscle.

8.7 Conclusions

Ergot alkaloids have biotechnological relevance due to their use as medicinal agents and to their role as toxins in agricultural industry. Future research on biotechnological aspects of ergot fungi will therefore most probably focus on the following trend analysis of biosynthetic pathway at enzymatic and genetic level. Alternatively, construction of recombinant peptide synthetases containing the D-lysergic acid-activating module should be a means to produce recombinant ergot drugs. With the availability of the ergot alkaloid biosynthesis gene cluster from *C. purpurea*, it will become possible to determine the regulatory mechanisms directly at the molecular level. This will be of importance for the improved biotechnological production of alkaloids in genetically engineered, alkaloid high-producing strains of *Claviceps*. In summary, detailed biochemical and molecular genetic research covering the various

aspects of ergot alkaloid-based drug development and control of toxins is required in the future. As these new studies move forward, it is hoped that this present paper will be a roadmap for also securing the data missing from our knowledge of the pharmacology of ergot alkaloids in particular *Claviceps purpura*.

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