Pharmacology of Cocaine

Chemically, cocaine is a [1R, 2R, 3S, 5S]-3-(benzoyloxy)-8-methyl-8-azabicyclo-[3.2.1] octane-2-carboxylic acid methyl ester, or the methyl ester of benzoylecgonine. It appears as cocaine base (CAS-50-36-2) and the hydrochloride salt (CAS-53-21-4). There the three components of the molecule, the dotted lines around each component in the drawing mark important parts: ecgonine, methyl alcohol, and benzoic acid (Fig. 30).

Cocaine is still classified as a narcotic by the federal government. It is found in Schedule II of the Controlled Substances Act of 1970, and is subject to all the restrictions placed on opioids also found in Schedule II. Cocaine is at present only approved for topical administration. Its primary use is in ENT surgery, particularly of the nose, pharynx, etc. The esters and derivatives of ecgonine, which are convertible to ecgonine and cocaine, are also controlled according to that Convention. Coca leaf is separately listed in Schedule I and is defined by Article 1, Paragraph 1, as: "The leaf of the coca bush, except a leaf from which all ecgonine, cocaine and any other ecgonine alkaloids have been removed". Cocaine is part of the alkaloids contained in the leaves (folia coca) of the coca bush Erythroxylon coca. It is a white, crystal-like powder, and when in the form of crack, cocaine base usually occurs as small (100–200 mg) lumps ('rocks').

Pharmaceutical Cocaine

A process perfected in the 1880s for extracting and purifying cocaine is known as the "Ecgonine Conversion Process". Rather than isolate just the natural cocaine alkaloid from the coca leaf, this process is designed to isolate only those alkaloids, which contain ecgonine, and to recover from them only the ecgonine portion of their molecules. To make cocaine from ecgonine; methanol and benzoyl chloride are added. Direct synthesis of cocaine was achieved in 1902 by Willstatter, but is a difficult process, and not commercially practical.

E. Freye, *Pharmacology and Abuse of Cocaine, Amphetamines, Ecstasy and Related Designer Drugs*,
DOI 10.1007/978-90-481-2448-0_8, © Springer Science+Business Media B.V. 2009

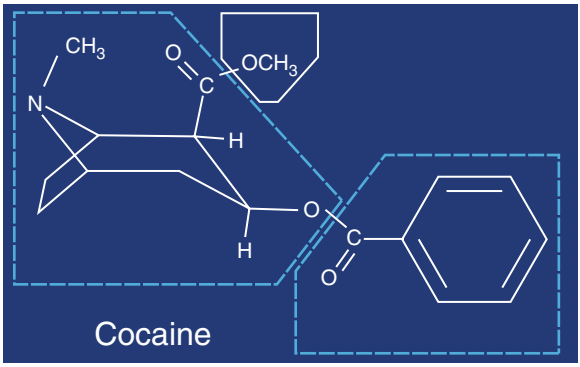

Fig. 30 The molecular structure of cocaine. Only one of its optically active isomers, commonly termed L-cocaine, occurs naturally

Table 6 Summary of the physicochemical properties of cocaine

Appearance	Color- and odorless, bitter taste, crystal like powder
Molecular weight	303.4 g/mol
Chemical formula of the base	$C_{17}H_{21}NO_4$
Melting point	Cocaine hydrochloride 197ºC Cocaine base 98ºC
Solubility of the base	Good solubility in ether Not soluble in water Good solubility in water (1,800 mg/ml-20ºC) Solubility of the salt Fair solubility in alcohol, chloroform, insoluble in ether
Metabolism	Pseudocholinesterase of blood plasma, liver enzymes (CYP34A)
Mean distribution half time mean time till max. onset of action, nasal	15–20 min
Mean plasma half time mean duration of action, nasal	1–2.5 h
Bioavailability	Oral: 33% Nasal: 19%
Excretion	Renal benzoylecgonine and ecgonine methyl ester

Physicochemical Properties of Cocaine

Cocaine has the following physiochemical properties as outlined in Table 6. Its major breakdown product is benzoylecgonine, which appears in greatest quantity in the urine, and consequently this is what it is tested for. Cocaine itself appears in varying quantities from 5% to 20% in its unchanged form in the urine.

Decomposition of Cocaine

Decomposition of cocaine is mainly by means of pseudocholinesterase of the blood and partly by liver enzymes [4] resulting into a number of metabolites (Fig. 31) such as ecgonidine, norecgonidine methyl ester, norecgonine methyl ester, and m-hydroxy-benzoylecgonine [5]. Among these (Fig. 32), benzoylecgonine methy lester is the major metabolite, which is formed both nonenzymatically as well as through the action of esterases found in a number of tissues including hepatocytes, the enzymatic mechanism being the dominant one [6], after which the metabolite is excreted via the kidneys [7, 8].

The simultaneous administration of cocaine and alcohol results in a pharmacological interaction at pharmacodynamic and pharmacokinetic levels. The latter involves an alteration of cocaine kinetics and metabolism, as well as the biosynthesis of newly active metabolites, such as cocaethylene [9]. Cocaethylene is metabolized along the same pathways as cocaine (Fig. 33). Its detection in biological samples indicates the combined consumption of cocaine and alcohol. During the interaction of both substances, the rise in cocaine plasma concentrations can explain many of cardiovascular [10, 11] and behavioral effects observed [12].

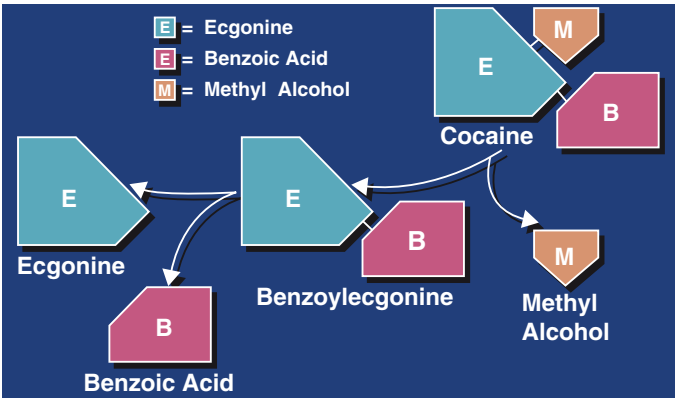

Fig. 31 The primary pathways in the decomposition of cocaine to its main metabolite benzoylecgonine, which can later be traced in an urine analysis

Cocaine, as a Local Anesthetic: Mechanism of Action

Cocaine's use as a local anesthetic had been promoted by Koller since 1884. The mode of action is that in the resting state, an equilibrium is reached when the axon interior

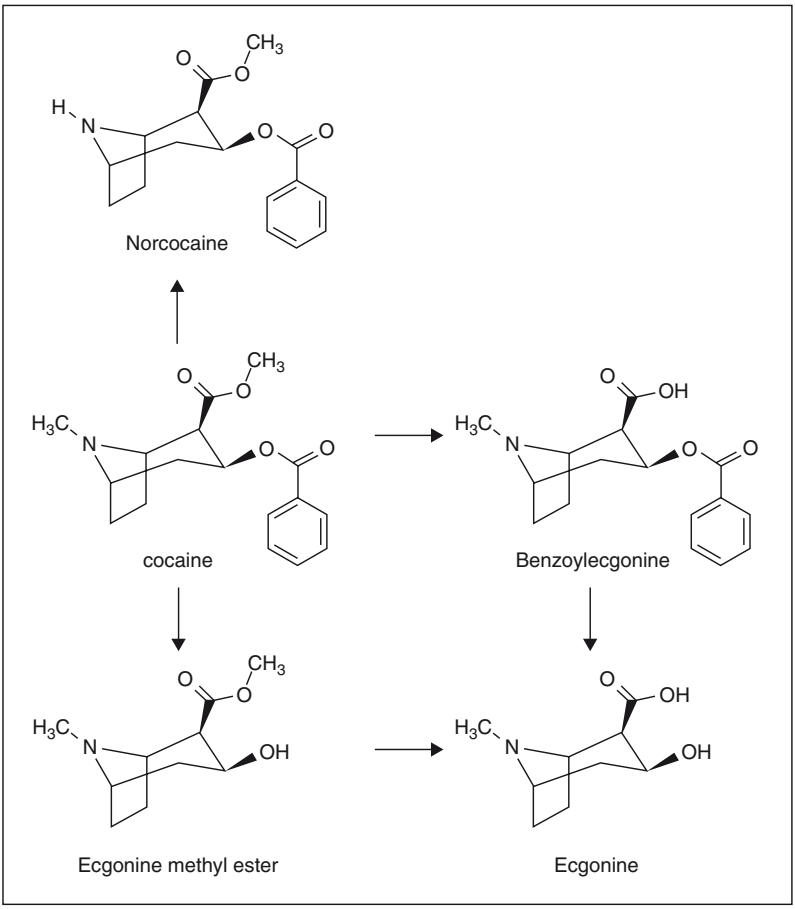

Fig. 32 Molecular structure of the different metabolites of cocaine being formed by pseudocholinesterase and liver enzymes

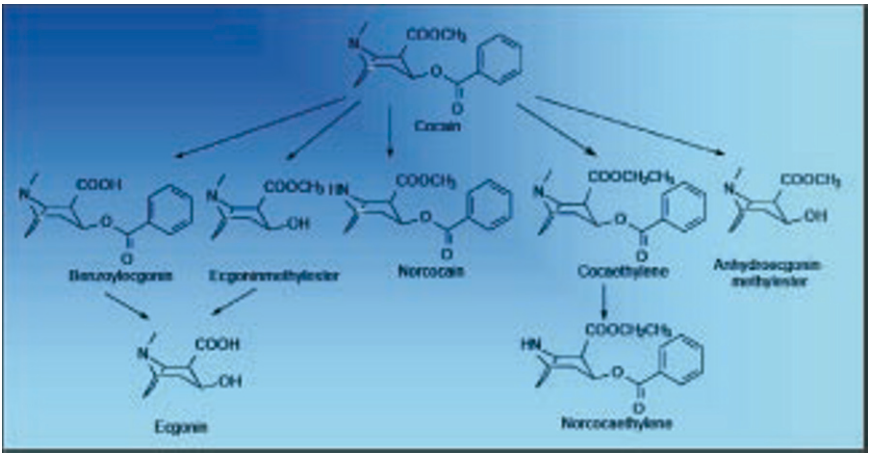

Fig. 33 Formation of cocaethylene when cocaine is ingested together with alcohol

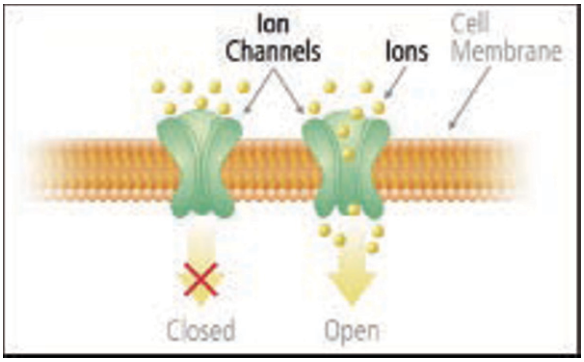

Fig. 34 Cocaine prevents migration of sodium ions into the axon of the nerve cell during stimulation of the nerve. This prevents the sodium ions from changing the electrical charge across the membrane and thus prevents the nerve from an action potential

is negatively charged with respect to the exterior. When the nerve is stimulated, activation gates in the sodium channels of the membrane begin to open, allowing sodium ions to migrate into the axoplasm, or inside of the cell. This causes the voltage difference to be reduced between the inside and outside of the axon. As sodium channels are then closed by inactivation gates, other ions move out of the axon to repolarize the membrane. Cocaine blocks the sodium channel preventing sodium ions from passing into the axoplasm (Fig. 34). This effectively prevents the sodium ions from causing a reduction of the voltage difference between the inside and outside of the axon, and this inhibits conduction of the nerve impulse.

Cocaine is available today from several manufacturers (DuPont, Merck Pharmaceuticals, Roxane, Mallinkrodt). Crystals are available from Mallinkrodt for preparing topical solutions. Most commonly, however, cocaine is packaged as premixed solutions of 4% and 10% containing 40 mg/ml and 100 mg/ml respectively, for Topical Solutions (Roxane; Fig. 35). These solutions are strictly for topical use only. However, they have been known to be used orally as adjuncts to opioids in the management of severe pain.

Cocaine is the only local anesthetic agent with vasoconstricting properties. This makes it especially useful to ENT procedures. Other (synthetic) local anesthetics usually must be combined with a vasoconstrictor such as epinephrine to keep their action localized to the site of surgery. While cocaine gained fame early as an anesthetic for eye surgery, it was later discovered that it causes clouding and pitting of the cornea and, in some cases, ulceration as well. It is because of these side-effects that topical cocaine solutions are not for ophthalmic use! Due to this, and the concern over systemic toxicity, cocaine has largely been replaced by synthetic agents such as lidocaine, bupivacaine, levobupivacaine, ropivacaine, tetracaine and/or procaine, all of which show a similar basic structure of an amino group linked via a carbon atom with an aromatic group (Fig. 36).

Fig. 35 Although being replaced by synthetics and being a scheduled II drug, use of a premix solution of cocaine is still available, strictly for topical anesthesia as a topical agent in ENT surgery

Cocaine's CNS Effects: Mechanism of Action

Of perhaps more interest than the local anesthetic effects of cocaine are the CNS effects, for it is this area that is responsible for the widespread popularity of cocaine as a substance of abuse (Fig. 37). Being also acclaimed as a cure for morphine and other dependencies, Freud was one of the first to experiment with cocaine on his friend Ernst von Fleischl-Marxow (Fleischl), morphine dependence, who suffering from neuropathic pain from an amputated thumb. At the same time countless patent medicines and tonics containing cocaine were available.

The central nervous effects of cocaine are related to the neurotransmitters norepinephrine and dopamine, which are normally released from presynaptic vesicles, diffuse across the synaptic cleft and bind with receptors on a receiving neuron. Excess norepinephrine (or dopamine) is then re-uptaken into the presynaptic vesicles for later use. Cocaine has the ability to block the re-uptake mechanism, preventing the re-absorption of the neurotransmitter. This results in higher

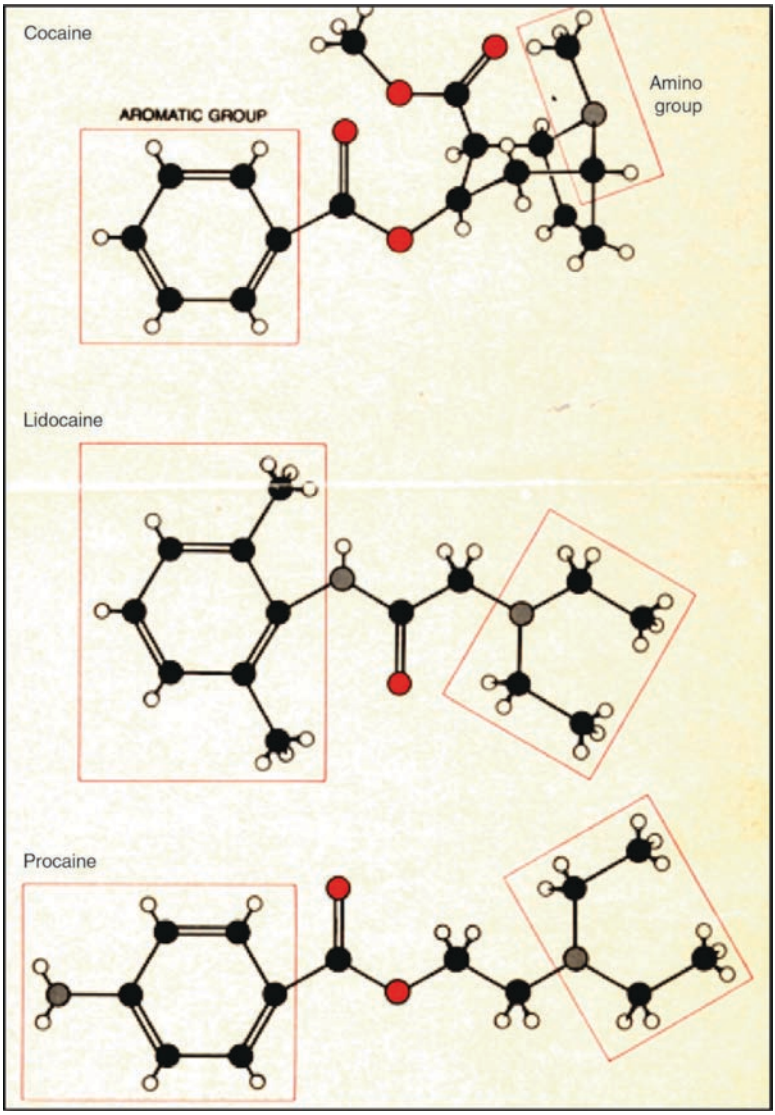

Fig. 36 Similarities in molecular structure of cocaine and two widely used local anesthetics

concentrations of the neurotransmitters norepinephrine and dopamine remaining in the synaptic cleft, which in turn bind to more post-synaptic receptor sites (Fig. 37).

Such an excess of neurotransmitters results in a concomitant overload at the receiving neuron, which then fires more frequently.

Primarily, euphoria is an effect of cocaine use and it is the one that gets all the attention anyway. There are however, some other important effects: increase in awareness; probably due to increased catecholamine activity. This along with euphoria is probably caused by alteration of dopaminergic activity in the limbic system. Tachycardia,

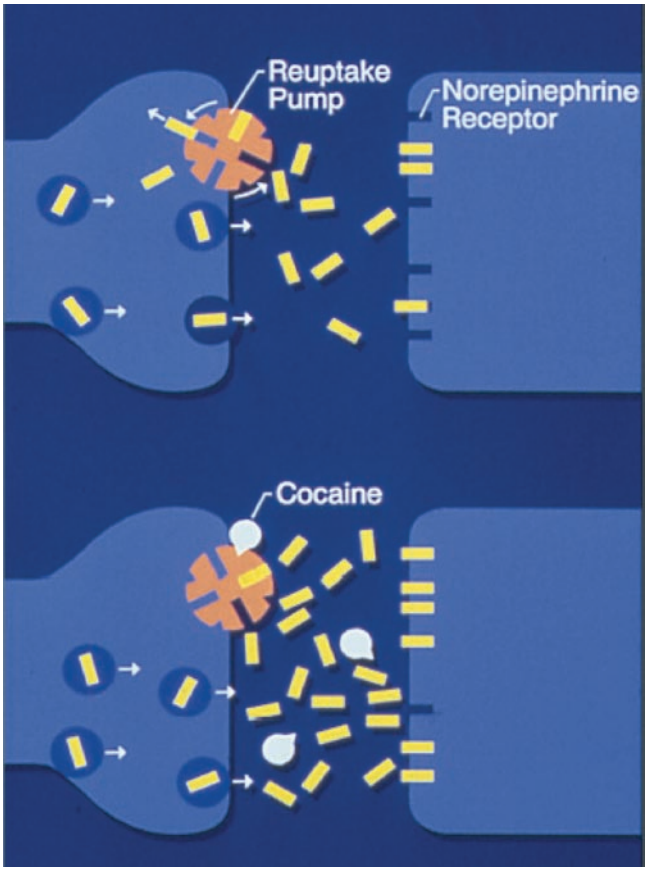

Fig. 37 Cocaine acting presynaptically as a reuptake inhibitor at the dopaminergic, serotinergic, and noradrenergic transmitter system

increased blood pressure and respirations are likely due to stimulation of norepinephrine, resulting in an "overamped" CNS (Fig. 38; Table 7). Anorexia seems to go hand-in-hand with CNS stimulants, and is one of the effects seen with chewers of the coca leaf, where coca was used to "deaden man's hunger and thirst".

Table 7 Summary of effects of cocaine on the sympathomimetic system

CNS effects of cocaine
Euphoria
Sensory awareness is increased
Higher state of vigilance
Tachycardia
Blood pressure rises
Anorexia
Respiratory increase
Mind widening
Increase in creativity
Reduced need for sleep

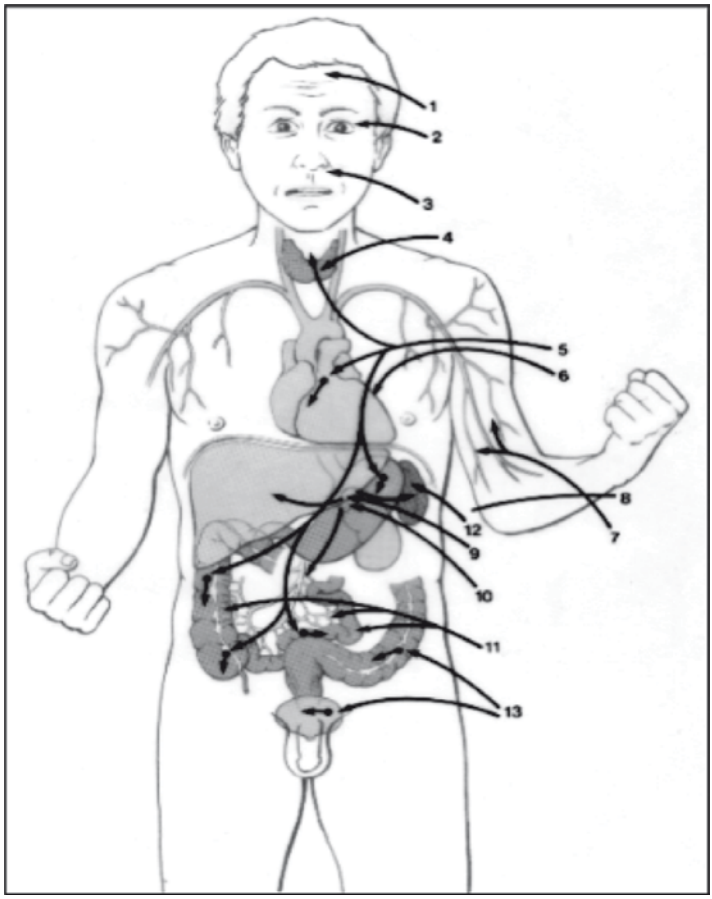

Fig. 38 Consequences by cocaine ingestion resulting in a "fight or flight reaction" with CNS activation (effects 1–12 see below)

In summary, cocaine will induce the following effects

1. Increase in vigilance with activation of defense mechanisms from the limbic system, reduced need for sleep
2. Mydriasis
3. Nasal drip
4. Release of thyroid hormone followed by glucose release
5. Coronary vessel constriction
6. Supraventricular tachycardia, increase in myocardial contractility, increase in blood pressure
7. Vasodilatation with increased muscle perfusion
8. Vasoconstriction of blood vessels of skin

9. Release of epinephrine and norepinephrine
10. Mobilization of glycogen from muscle and liver
11. Inhibition of motility and reduced perfusion of stomach and small intestine and inhibition of digestive function
12. Increase in muscle tone of the large intestine

Concerning the autonomic nervous system, Erlanger and Gasser stated: "Cocaine enhances the response of the innervated structures of the sympathetic system, as well as epinephrine and norepinephrine, both sympathetic chemical transmitters. In this way, they provoke vessel constriction, mydriasis and tachycardia being related as sympatho-mimetic actions. It is for this reason, that medium cocaine doses produce tachycardia and an increase of blood pressure on the heart. And, as in every excess, high doses revert their action and blood pressure can decrease intensely". This mechanism of action of cocaine as a stimulant is based on the blockade of recapturing norepinephrine in the synaptic cleft. Once the mission of the neurotransmitter norepinephrine, which is in charge of carrying the message via the synaptic cleft to the other cell, has been accomplished, it is degraded by special enzymes or recaptured. The cocaine molecule blocks the recapturing of the neurotransmitter, forcing it to remain in the synaptic cleft for a longer period of time and continue its stimulating action (Fig. 37). When used over a long period of time, another clinical effect is related to blockade of re-uptake of neurotransmitters. Such long-term prevention in re-uptake can cause depletion of the neuron's supply (Fig. 39), and it is this phenomenon that is theorized to account for the depression and craving associated with the cessation of cocaine use.

Emotional Effects of Cocaine

Since Sigmund Freud popularized the uptake of cocaine crystals prepared by the Merck Laboratories (Fig. 18), through the nasal mucous membrane, other possible ways of administration were set aside for reasons not too well determined. This was in spite the fact that he himself, due to injuries in his nasal passages, resorted to oral absorption dissolving the powder in water to drink. Actually, the application of the powder in any of the mucous membranes (nasal, oral, genital, anal) has the same speed of absorption. However, nasal aspiration continues to be the preferred method for easier administration. A quantity of 60 mg dispensed through the nasal mucosa, after entering the brain circulatory system, produces a general increase of body energy. Metabolism accelerates in proportion to the dose, just as the physical, intellectual activities and the emotional tone increase. Cardiac frequency and blood pressure also rise slightly. Respiratory frequency and volume are also increased thus requiring a greater oxygen intake. Aside from such acceleration of physiological functions, hunger and tiredness sensations disappear. There is an increase of intestinal peristalsis, which, however, is not observed in coca chewing, and results in lesser assimilation of nutrients. The latter, in association with the increase of metabolism, individual

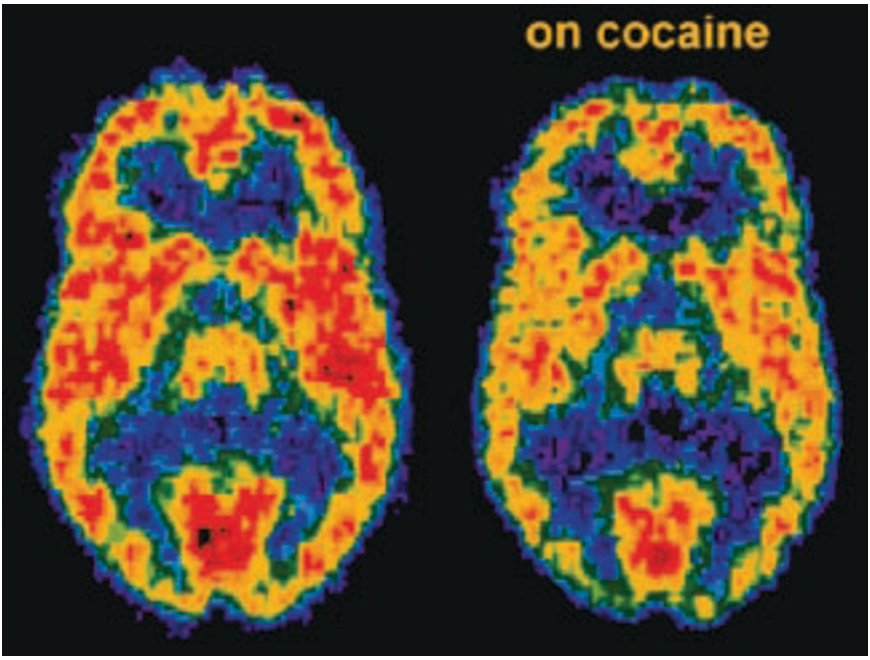

Fig. 39 PET scan showing how the use of cocaine interferes with glucose-metabolism in the brain. The dark color denotes the highest level of glucose utilization as seen for the normal brain on the left. Yellow represents less utilization and blue the least utilization. Glucose provides energy to neurons and when those neurons cannot use glucose, many brain functions will be disrupted

activity and the anorexia effect, explains the success achieved in weight reducing treatments. In addition to snorting and intravenous use, sublingual application has also been reported [13], where street cocaine (cocaine hydrochloride) is mixed with baking soda and placed under the tongue. Since the more neutral the pH of that mixture the higher absorption through the capillary bed under the tongue resulting in better titration to effect with lesser transitions between highs and lows (crashes), less interference with eating and sleeping and lastly, no nasal drip as usually experienced after snorting.

Aside from physiological functions, emotional areas are also stimulated (Fig. 39). There is a pleasant peaceful feeling, and at higher doses one feels euphoria and enthusiasm. The user feels content, loquacious (talkative), uninhibited and courageous. If there were emotional depressions before, it subsides rapidly, giving way to positive feelings about life in general. In regard to the psychological effects, one can observe an acceleration of all higher mental functions, such as capacity for thought course and association of ideas. The individual is wide-awake, and sleep can be postponed. The capacity for abstraction, concentration, attention and memory improves. The content of thoughts is enriched and fantasizing or having more optimistic and pleasant ideas about life are facilitated. Sensorial perception becomes

keen and sensitive. In respect to sexual activity, cocaine has very definite aspects. It increases sexual desire and potency notoriously, however, chronic cocaine users show a significant decline in sexual behavior.

The two-sided and sometimes schizophrenic opinion of the society regarding the use of cocaine is reflected in the media. While there are articles describing the devastating effect of long-term use and abuse, in the late 1970s the use of cocaine by championship athletes was associated with manliness and power. Cocaine became the media's powdery star with stories of its use by the famous, its increasing expense and its description as the caviar or champagne of drugs. In July 1981 Time magazine showed a champagne glass full of sparkling white powder with the headline "HIGH ON COCAINE- a drug with status- and menace". The net effect of the article was a positive and alluring image of cocaine. In New York magazine (1978) cocaine was referred to as "the drug of choice" and "every bit as enjoyable as Freud claimed": "Cocaine is God's way of telling you that you've made too much money."