

Lecture 7: Cocaine and other sympathomimetics

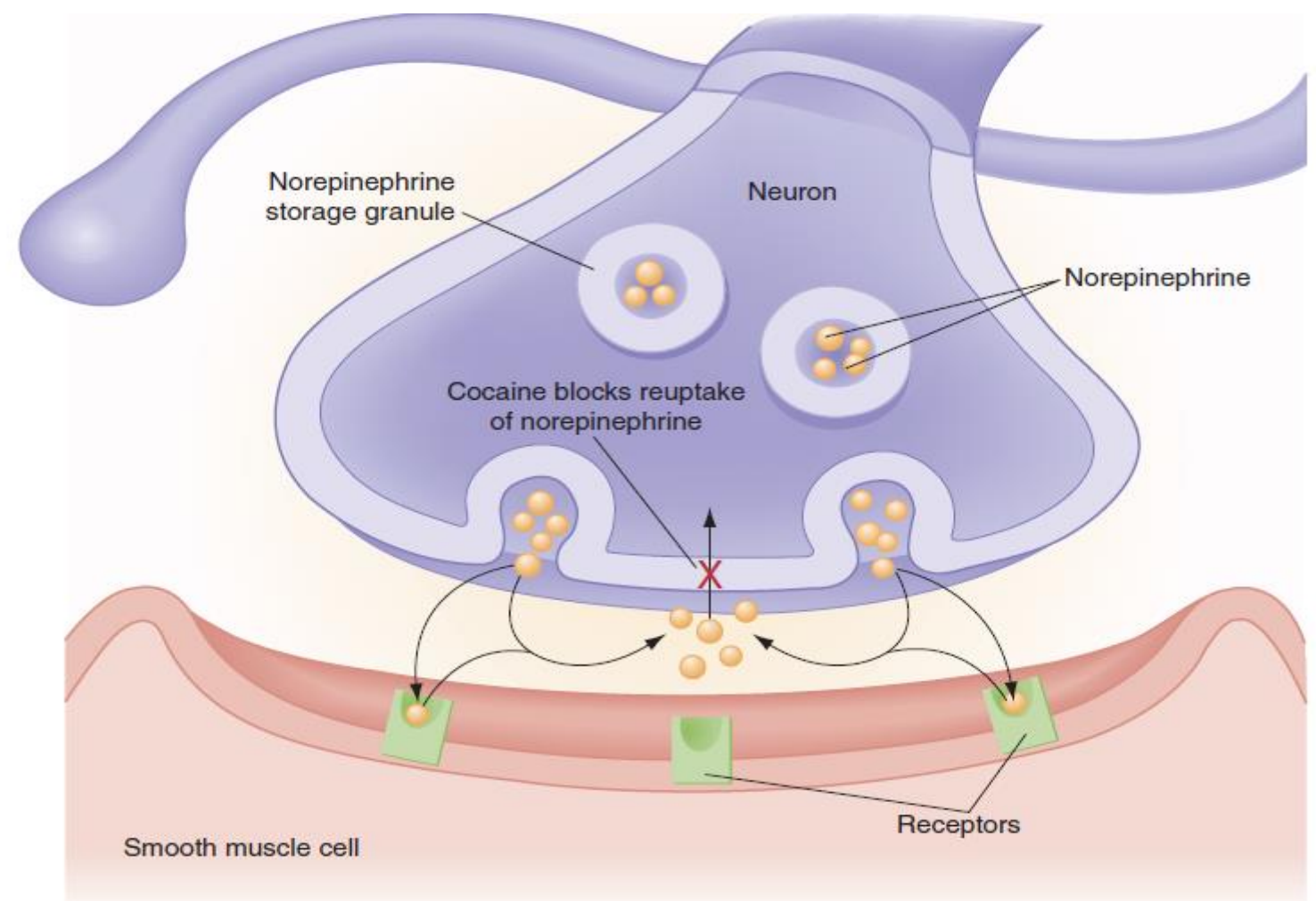
Introduction:

What are they?

Cocaine, amphetamines, and derivatives of amphetamines are called sympathomimetics.

These agents cause central nervous system (CNS) stimulation and a cascade of physiologic effects.

Cocaine → release of catecholamine (epinephrine, norepinephrine & dopamine) and serotonin → vasoconstriction



Pathophysiology

Acute cocaine use causes release of **dopamine, epinephrine, norepinephrine, and serotonin**. Most important effects are adrenergic stimulation by **norepinephrine and epinephrine**.

Summary

- 1: Norepinephrine causes vasoconstriction** by stimulating alpha-adrenergic receptors on vascular smooth muscle.
- 2: Epinephrine increases myocardial contractility** and heart rate through stimulation of beta1-adrenergic receptors.
- 3: In addition to causing catecholamine release, the reuptake of these stimulatory neurotransmitters from synaptic clefts is inhibited**, altering the normal balance between excitatory and inhibitory tone in the CNS. The only sympathomimetic that causes inhibition of the reuptake is Cocaine!
- 4: Cocaine also is a local anesthetic agent, slowing nerve impulses from neuronal pain fibers by blocking the inward movement of sodium across cell membranes** (phase 0 of the action potential).
- 5: Sodium channel blockade across myocardial cells, similar to the class IA antidysrhythmic agents (as procainamide and quinidine)**, irresponsible for the occasional conduction abnormality with acute cocaine toxicity.
- 6: Cocaine metabolism occurs in the liver and the plasma.**

Pathophysiology

Action	Receptor	effect
Release Norepinephrine	alpha 1 (main effect)	Vasoconstriction
Release Epinephrine	beta 1 (main effect)	Increase myocardial contractility + increase heart rate (tachycardia)
Inhibition reuptake of catecholamine	alpha2	
Blocking Na inward (phase 0 action potential)	Sodium receptors in pain nerves	Local anesthetic agent Conduction abnormality in myocardial cells

Metabolites

- Cocaine metabolism occurs **in the liver and the plasma**.
- In the liver, primarily to the active metabolite norcocaine, which potentiates the parent drug.
- In the plasma, to ecgonine methyl ester via pseudocholinesterase (plasma cholinesterase). *If pseudocholinesterase is deficient, cocaine intake will cause sudden cardiac arrest.*
- Ecgonine methyl ester may be protective because it is a vasodilator.
- **Benzoyl ecgonine is a metabolite found in the plasma and is the metabolite identified by urine toxicology screens.**
- The use of ethanol with cocaine may form coca ethylene, a metabolite that may potentiate the drug's stimulatory effects.

Clinical features

Excitation of the sympathetic nervous system.

* Patients with moderate toxicity are alert and awake but may have , **diaphoresis, tachycardia, mydriasis, and hypertension without organ damage.**

* A more severely intoxicated patient may present agitated, combative, and **hyperthermic.**

* Signs and symptoms of **end-organ damage may be present, including acute hypertensive emergencies.**

* Patients may present with focal, **acute pain syndromes; circulatory abnormalities; delirium; or seizures.**

More toxic dose

Alert, diaphoresis, tachycardia, mydriasis, and hypertension without organ damage.

Agitated, combative, and hyperthermic.

End-organ damage (acute hypertensive emergencies).

- Patients may present with focal, **acute pain syndromes**; circulatory abnormalities; **delirium**; or seizures.
- The clinical presentation depends on the dose, route of administration, and time to presentation after drug use.
- Patients who are “speed balling,” using IV heroin (**morphine**) and cocaine together, may be **initially sedated**, and **administration of naloxone may reveal the underlying cocaine intoxication.**
- Mortality is high with temperatures greater than 41.1°C.

Clinical features

Common presentation according to the system		
Cardiac	Tachycardia, arrhythmia (sinus tachycardia most common), Hypertension, angina & endocarditis (for IV)	Hypertension
Respiratory	Tachypnea, septal necrosis or sinusitis and naso palatine necrosis or perforation (intranasal), pnemothorax, pneumomediastanium, aspiration pneumonia	Hyperthermia
GIT	Constipation	Tachycardia
CNS	Agitation & delirium	Mydriasis
Endocrine	Hyperthermia	Diaphoresis
		Central nervous system excitation

Common Method of sympathomimetic abuse

- Inhalation
- Intranasal
- Intravenous (fastest onset of action)
- Oral
- Skin popping (injection of drugs subcutaneously or intradermally.)

ROUTE	FORMULA	ONSET OF ACTION	PEAK EFFECT	DURATION
Inhalation	“Crack”	8 sec	2–5 min	10–20 min
Intranasal	Cocaine HCl	2–5 min	5–10 min	30 min
Intravenous	Cocaine HCl	Seconds	10–20 min	60–90 min
Oral	Cocaine HCl	30–60 min	60–90 min	Unknown
“Skin popping”	Cocaine HCl	Unknown	Unknown	Unknown

Complication

Initial assessment and treatment should focus on rapidly fatal complications :

Arrhythmia:

- **Sinus tachycardia** is the most common but other forms of arrhythmia (AF & supraventricular tachycardia) could happen.
- **ECG: Torsades de pointes or wide-complex tachycardia**
- **Happens due to sodium channel blockage.**
- **Treatment: sodium bicarbonate (first line of treatment) & lidocaine .**

Hyperthermia:

- **Increased motor tone can release intramuscular (CK) with rhabdomyolysis and renal and electrolyte complications.**
- agitation + delirium → ↑ the risk of hyperthermia.
- Best route to assess the temperature is **rectal**.
- **Treatment:** for severe active cooling.

Hyperthermia classification

Mild: 37.3-38.4

Moderate: 38.5-39.9

Severe > 40

Hypertension crisis:

- **Complication of hypertension:** Aortic dissection, pulmonary edema, myocardial ischemia and infarction, intracranial hemorrhage, strokes, infarction of the anterior spinal artery, retinal vasospasm, renal infarctions, placental insufficiency and infarction in the gravid uterus.
- Intestinal infarctions & mesenteric ischemia in body packers.
- **Treatment: phentolamine** (Alpha blockers) (DO NOT GIVE BETA BLOCKERS)

Seizure:

Treatment: Benzodizapan (diazepam lorazepam midazolam)

Complication

Rhymbdomyolysis :

- **Due to Hyperthermia or myocardia infarction**
- **Investigation:** high Creatinine kinase (CK), hyperkalemia
- **Complications:** Acute kidney injury
- **Treatment:** Fluids

Other complications:

- **Crack dancing:** a transient choreoathetoid movement disorder.
 - **DVT:** secondary to effects on coagulation.
 - **oropharyngeal burns:** due to high temperature required to volatilize the drug.
 - **Botulism, endocarditis:** intravenous users
 - **Pneumothorax, pneumomediastinum & pneumomediastinum:** from inhalational barotrauma.
 - **Sinusitis, naso-palatine necrosis or perforation :** intranasal cocaine
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Diagnosis criteria

Usually diagnosed by toxic syndrome and history but could use some further tests to confirm.

Urine test:

- Cocaine is metabolised to **benzoylecgonine** and excreted in the urine (present for 3 days after last use)
- Used for : (1) to document possible abuse
(2) to confirm cocaine as the unknown substance in body packers
(3) to differentiate paranoia from drug-induced or psychiatric causes.

ECG: Torsades de pointes or wide-complex tachycardia.

Creatine kinase (CK): serum CK-MB fraction, troponin I, and troponin T are more specific in patients with atherogenic coronary disease.

Urinalysis: should be checked for myoglobin, which indicates rhabdomyolysis.

Chest radiograph : to identify aspirated foreign body, pneumothorax or pneumomediastinum .

Differential diagnosis for sympathomimetic toxicity

Sedative-hypnotic withdrawal

Amphetamines and its derivatives

Infection

Anti-cholinergic (Diaphoresis in sympathomimetic)

Thyrotoxicosis

Management :

Initial evaluation of patients with sympathomimetic stimulation

Rapid assessment of vital signs, especially core temperature (with physical restraints to secure IV access)

Rule out hypoxia, hypoglycemia (or IV dextrose and thiamine)

Pharmacologic sedation with IV benzodiazepines

ECG

Urinalysis

Serum creatinine phosphokinase

- **Hyperthermia:** active cooling + aggressive fluid resuscitation.
- **Hypertension:** **Phentolamine** (alpha-adrenergic antagonist) , beta blockers cause paradoxical hypertension.
- **Dysrhythmias:** **IV sodium bicarbonate**. Lidocaine & amiodarone for ventricular dysrhythmias.

Cocaine-related chest pain:

- Cocaine induces coronary vasoconstriction and increase myocardial oxygen demand, benzodiazepines decrease myocardial oxygen demand by limiting peripheral stimulation.
- MI in ECG : coronary vasodilation with IV Phentolamine .
- Morphine sulfate is used to treat pain .
- Beta blockers including Labetalol are contraindicated .

Some definitions

Body packers:

- Those who ingest cocaine that has been wrapped tightly into condoms or latex products and wax.
- Each packet can contain approximately 10 g of cocaine (which is fatal), and packers may swallow as many as 150 packets.
- A body packer may present without symptoms to the ED, but should be placed immediately on continuous cardiac monitoring, with large-bore IV access.
- An abdominal radiograph may confirm foreign bodies, When uncertainty persists, a contrast study is warranted.

When evidence of cocaine toxicity is manifest, rapid transportation to the **operating room** may be the only way to save these patients.

Benzodiazepines, neuromuscular blockade, or sodium bicarbonate administration may be required en route.

Body stuffers:

- A “body stuffer” is an individual who attempts to conceal evidence of cocaine possession by swallowing the drug while pursued by law enforcement officials.
- These are usually unplanned events with generally small quantities of drug intended for personal use.

Other stimulants

Amphetamin:

- Enhance release of catecholamines from presynaptic nerve terminals, do not block sodium channels and only minimally affect presynaptic reuptake of catecholamines.
- CNS stimulation results in nearly identical sympathomimetic effects to those from cocaine, but not with the same frequency or intensity.
- Patients are at risk for Hyperthermia, hypertensive emergencies, Dysrhythmias, myocardial ischemia, hyperkalemia associated with rhabdomyolysis.
- Although urine drug screens can identify amphetamines, they are of little utility in treating an intoxicated patient.
- The management follows the same guidelines as for cocaine, although the duration of toxicity tends to be longer for amphetamines.

Other stimulants

Methylenedioxymethamphetamine :

- Methylenedioxymethamphetamine (MDMA—“Ecstasy,” XTC, Adam) is a chemically modified amphetamine originally taken orally at all-night dance parties which cause life-threatening hyponatremia.
- urine samples with a relatively high urine sodium level, similar to SAIDH.
- Unless seizures or other neurologic events are present, patients can be treated supportively with fluid restriction.
- Normal saline or other crystalloids may worsen the hyponatremia because these patients are likely to retain more free water than sodium.
- Their fluid intake should be restricted unless severe hypovolemia exists, and they should be treated with hypertonic saline for neurologic impairment.
- In contrast to other amphetamines, chronic MDMA use causes potentially irreversible neurologic damage to serotonergic neurons.

Methamphetamine:

- Methamphetamine, known as “crank” and “crystal meth,” is a fat-soluble, smokable, designer amphetamine.
- Complications from methamphetamine use are similar to those from other sympathomimetics.
- The duration of action can be significantly longer, however, with some paranoid delusions persisting for 15 hours.

Summary :

- Rapid sedation with an IV benzodiazepine is the key for most symptoms from cocaine and other stimulants (should be the first thing to do).
- Hyperthermia increases mortality if it exceeds 41 degree.
- First line therapy of hypertension in cocaine abuser is Phentolamine.
- Use IV sodium bicarbonate or Lidocaine in cardiac dysrhythmia.
- Beta blockers are contraindicated in cocaine abuser.
- Symptomatic cocaine body packers need immediate surgery.
- Amphetamine symptoms and its effects last longer than those produced by cocaine.

MCQs

1) Which of these symptoms and signs would not be found in patients with cocaine overdose?

- A-Tachycardia
- B-Anhidrosis
- C-Mydriasis
- D-Hyperthermia

2) All these factors contribute in the generation of high body temperature (Hyperthermia) after cocaine toxicity except?

- A-Delirium
- B-Agitation
- C-Dehydration
- D-Vasodilation

3) A 30 year old male patient presents with an acute myocardial infarction. Which drug has MOST LIKELY caused this?

- A-Increased adrenalin production due to heroin
- B-Increased serotonin due to fluoxetine
- C-Increased noradrenaline effects of cocaine
- D-Monoamine oxidase inhibition by amphetamine derivative

4) A 28 year old IV drug abuser was brought by his brother to the emergency after finding him fallen with lost consciousness in the living room, the brother reported that the patient is a known cocaine consumer and had similar attacks in the past with a previous diagnosis of arrhythmias for many times, what is the pathophysiology behind that in this case?

- A-Overactivity of SA node due to sympathetic activation
- B-Blockage of Sodium funny channels
- C-Blockage of Potassium efflux channels
- D-Excessive levels of calcium in blood

5) Which one of these is not an indication for urine benzoyl ecgonine levels measurement?

- A-To exclude psychiatric causes of patient's symptoms
- B-To document a possible use of cocaine
- C-To confirm the use of cocaine in the past one week
- D-To determine the substance used in body packers

6) A patient with history of cocaine overdose ingestion was received in the ER very agitated, the patient was attacking the physician and preventing them to start managing him, which one of these classes of drugs may be used to sedate the patient?

- A-Benzodiazepines
- B-Halothane
- C-Barbiturate
- D-Melatonin

7) Which one of these statements is correct regarding Body Packers and Body Stuffers?

- A-First is swallowing the drug while pursued by law enforcement officials and latter is hiding the drug in their GI tract while before crossing international borders
- B- First is hiding the drug in their GI tract while before crossing international borders and latter is swallowing the drug while pursued by law enforcement officials
- C-Both cannot be discovered by abdominal radiograph
- D-Small quantity of the drug is ingested in both types

8) Which one of these is a characteristic of Methylenedioxymethamphetamine (MDMA) but not Amphetamine?

- A-A pro-arrhythmic agent
- B-Lead to hypertensive emergencies
- C-Neurological damage in chronic use
- D-An important cause of hyperthermia

Answers : 1(B) – 2(D) – 3(C) – 4(B) – 5(C) – 6(A) – 7(B) – 8(C)



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