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A Review On Various Properties of Methamphetamine

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Abstract

Methamphetamine is a potent central nervous system (CNS) stimulant belonging to the substituted phenethylamine and amphetamine class of compounds.

Its chemical structure, $C_{10}H_{15}N$, enables high lipid solubility and rapid passage across the blood–brain barrier, resulting in intense psychostimulant effects.

Pharmacologically, methamphetamine acts primarily by increasing synaptic concentrations of monoamine neurotransmitters dopamine, norepinephrine, and serotonin through the reversal of transporters and inhibition of reuptake mechanisms.

These actions produce heightened alertness, euphoria, and increased energy but also lead to severe neurotoxicity, cardiovascular stress, and addiction potential with chronic use.

Physically, methamphetamine is a white crystalline powder or solid that is soluble in water and alcohol, with a melting point of approximately 170–175°C.

Its optical isomers, d-methamphetamine and l-methamphetamine, differ in potency and pharmacological activity,

the dextro form being more psychoactive. Methamphetamine's chemical stability and ease of synthesis from common precursors have contributed to its widespread illicit production.

Ongoing research explores its limited medical applications—such as in the treatment of attention deficit hyperactivity disorder (ADHD) and obesity—while highlighting its significant social, health, and neuropsychological consequences.

1. Introduction

Methamphetamine ($C_{10}H_{15}N$) is a potent psychostimulant drug that exerts profound effects on the central nervous system (CNS) and has both medical and illicit significance.

Belonging to the substituted phenethylamine and amphetamine chemical class, it is the *N-methyl derivative* of amphetamine, a structural modification that increases its lipid solubility, facilitating rapid penetration of the blood–brain barrier (BBB) and resulting in greater potency and prolonged effects compared to its parent compound).

Methamphetamine occurs as two optical isomers: d-methamphetamine, the more psychoactive form, and l-methamphetamine, which has weaker central stimulant activity and limited clinical use as a nasal decongestant

Methamphetamine was first synthesized in 1893 by Japanese chemist Nagai Nagayoshi from ephedrine and later crystallized into a more stable form by A. Ogata in 1919. It was widely used during World War II to enhance alertness and reduce fatigue among soldiers

In the postwar period, methamphetamine's medical applications included the treatment of attention-deficit/hyperactivity disorder (ADHD), narcolepsy, and obesity due to its appetite-suppressant and wakefulness-promoting properties.

However, its high abuse potential and neurotoxic effects led to strict regulation under international and national drug control laws, with only limited therapeutic use today under the trade name Desoxyn.

Pharmacologically, methamphetamine acts as a potent central nervous system stimulant by targeting monoaminergic neurotransmission. It increases extracellular levels of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) primarily through the reversal of their respective transporters (DAT, NET, and SERT) and inhibition of vesicular monoamine transporter 2 (VMAT2).

This cascade results in an abnormal accumulation of dopamine in the synaptic cleft, leading to euphoria, increased energy, and heightened alertness. Over time, excessive dopamine release and oxidative stress cause dopaminergic neurodegeneration, manifesting as cognitive deficits, anxiety, psychosis, and motor dysfunctions similar to those observed in Parkinson's disease

The pharmacokinetics of methamphetamine further contribute to its potency and addictive nature. With a plasma half-life of approximately 10–12 hours, methamphetamine remains active significantly longer than other stimulants such as cocaine, resulting in sustained stimulation and compulsive drug-seeking behavior Metabolic processing occurs mainly in the liver via cytochrome pathways, producing amphetamine as a major active metabolite, while excretion depends strongly on urinary pH .

The combination of prolonged duration, high CNS penetration, and neurochemical reinforcement underpins its strong addictive potential.

On a social and epidemiological level, methamphetamine misuse represents a major global public health concern. According to the United Nations Office on Drugs and Crime methamphetamine remains one of the most commonly manufactured and trafficked synthetic drugs worldwide. Illicit production typically involves the reduction of precursor compounds such as ephedrine or pseudoephedrine, with clandestine laboratories posing serious environmental and safety hazards.

Chronic use is associated with a wide range of medical complications, including cardiovascular damage, dental decay ("meth mouth"), malnutrition, and psychiatric disorders such as paranoia, aggression, and hallucinations

Despite decades of research, there are currently no FDA-approved pharmacotherapies for methamphetamine dependence, and treatment remains largely behavioral, focusing on cognitive-behavioral therapy (CBT) and contingency management approaches As methamphetamine continues to pose challenges to both healthcare and law enforcement systems, a comprehensive understanding of its chemical structure, pharmacological mechanisms, and neurobiological consequences is crucial for developing effective prevention and intervention strategies.

CLASSIFICATION

- **Chemical class:** Phenethylamine
- **Sub-class:** Amphetamine derivative
- **IUPAC name:** (S)-N-methyl-1-phenylpropan-2-amine

- **Molecular formula:** $C_{10}H_{15}N$
- **Molecular weight:** 149.24 g/mol
- **Structure:** Contains a phenyl ring attached to a two-carbon chain with a methylamino group
- **Pharmacological class:** Central Nervous System (CNS) stimulant
- **Mechanism of action:** Increases release of monoamines (dopamine, norepinephrine, serotonin)

MORPHOLOGY

Physical Appearance:

- Typically found as a white, odorless, crystalline powder.
- Street forms may appear as small crystalline shards ("crystal meth"), or as powder with impurities.
- Commercial/pure form is hygroscopic (absorbs moisture from the air).

Crystal Structure:

- Methamphetamine hydrochloride forms monoclinic crystals.
- Crystals can range from fine powder to larger needle-like shards, depending on the synthesis method.

Solubility:

- Highly soluble in water, alcohol, and organic solvents.
- The free base form is less soluble in water but more volatile.

Molecular Structure:

- Phenethylamine backbone with a methyl group attached to the nitrogen atom.
- Chiral molecule: exists as d-methamphetamine (more potent CNS stimulant) and l-methamphetamine (weaker stimulant, found in some nasal decongestants).

Melting/Boiling Points:

- Methamphetamine hydrochloride melts at ~170–175 °C.
- Free base form melts at ~167–168 °C and is volatile at slightly higher temperatures.

Other Properties:

- Colourless to white in pure form.
- The crystalline form is brittle and glass-like.
- Can be converted between free base and salt forms depending on chemical processing.

CHEMICAL COMPOSITION

Chemical Composition of Methamphetamine

- Chemical formula: $C_{10}H_{15}N$
- Molecular weight: 149.24 g/mol
- Chemical class: Phenethylamine derivative (amphetamine class)

- Functional groups:
  Amine group (–$NHCH_3$): responsible for its CNS stimulant activity
  Phenyl ring (aromatic ring): contributes to lipophilicity and crossing the blood–brain barrier
  Alkyl chain (propyl group): adds to potency and bioavailability
- Forms:
  Methamphetamine hydrochloride (salt form): White crystalline powder, water-soluble
  Methamphetamine free base: Oil or crystal form, volatile, less water-soluble
- Stereochemistry:
  Chiral molecule:
  - d-methamphetamine (dextro) – stronger central nervous system stimulant
  - l-methamphetamine (levo) – weaker stimulant, found in some decongestants

INDUSTRIAL PRODUCTION PROCESS

Industrial Production of Methamphetamine (Legal/Pharmaceutical Context)

1. **Purpose and Regulation**
   Methamphetamine is legally produced only under strict regulatory control for medical purposes, such as ADHD and narcolepsy treatment (e.g., Desoxyn® in the U.S.).
   Production occurs in pharmaceutical manufacturing facilities under Good Manufacturing Practice (GMP) standards.
   The process is heavily monitored for purity, stereochemistry, and safety.
2. **Chemical Basis**
   Methamphetamine is a phenethylamine derivative.
   Industrial synthesis uses precursors such as ephedrine or pseudoephedrine in controlled chemical reactions.
   The focus is on producing the dextro isomer (d-methamphetamine), which has the desired CNS stimulant activity.
3. **Forms Produced**
   Methamphetamine hydrochloride (HCl): White crystalline powder, water-soluble, suitable for oral administration.
   Tablet or capsule formulations: Standardized doses for medical use.
4. **Quality Control**
   Purity testing: High-performance liquid chromatography (HPLC), gas chromatography (GC), and mass spectrometry (MS).
   Stereochemistry verification: Ensures the active d-isomer is predominant.
   Contaminant testing: Ensures removal of solvents, residual reagents, and by-products.
5. **Safety Measures**
   Industrial production requires controlled environments, protective equipment, and proper ventilation.
   Waste and by-products are disposed of according to hazardous chemical regulations.
   TRADITIONAL USES

Medical Uses (20th Century to Present)

- Treatment of narcolepsy: Improves wakefulness and reduces excessive daytime sleepiness.
- ADHD (Attention-Deficit/Hyperactivity Disorder): Stimulates CNS activity to improve attention and focus.
- Obesity/weight management: Historically prescribed as an appetite suppressant (less common today due to abuse potential).

Military Use

- World War II and later: Amphetamine derivatives, including methamphetamine, were used by military forces to reduce fatigue and increase alertness in soldiers.

Non-medical Historical Use

- Early 20th-century over-the-counter stimulants: Amphetamine tablets, including methamphetamine in some countries, were sold for alertness, mood elevation, or fatigue reduction.
- Misuse became widespread after World War II due to easy accessibility.

Current Legal Medical Use

- In modern medicine, methamphetamine is highly controlled.
- Marketed as Dioxin® in the U.S. for ADHD and narcolepsy, under strict prescription regulations.

PHARMACOLOGICAL ACTIVITY

1. **Class and Mechanism of Action**
    - Pharmacological class: Central Nervous System (CNS) stimulant, sympathomimetic amine.
    - Primary mechanism:
        - Methamphetamine increases the release of monoamine neurotransmitters: dopamine (DA), norepinephrine (NE), and serotonin (5-HT).
        - It blocks reuptake transporters (DAT, NET, SERT), leading to elevated synaptic concentrations.
        - Promotes reverse transport of dopamine, causing massive release into the synaptic cleft.
2. **Central Nervous System Effects**

    Stimulation: Increased alertness, energy, and wakefulness.
    Euphoria: Dopaminergic surge in the mesolimbic “reward pathway” of the brain.
    Cognitive effects: Short-term improvements in attention and focus; chronic use leads to cognitive deficits, memory impairment, and neurotoxicity.
    Addiction potential: High; repeated use leads to tolerance, dependence, and compulsive drug-seeking behavior.
3. **Peripheral (Autonomic) Effects**

    Cardiovascular stimulation: Increased heart rate, blood pressure, and cardiac output.
    Respiratory stimulation: Mild increase in breathing rate.
    Metabolic effects: Increased basal metabolic rate and decreased appetite.

4. **Other Pharmacological Effects**
   Sympathomimetic effects: Mydriasis (pupil dilation), sweating, vasoconstriction.
   Appetite suppression: Due to CNS-mediated anorectic effect.
   Neurotoxicity (chronic use): Oxidative stress and damage to dopaminergic and serotonergic neurons.
5. **Pharmacokinetics**
   Absorption: Rapid via oral, inhalation, or intravenous routes.
   Distribution: Highly lipophilic; crosses the blood–brain barrier efficiently.
   Metabolism: Primarily in the liver via CYP2D6.
   Excretion: Mostly via urine; pH-dependent renal clearance.
   Half-life: ~10–12 hours (varies with pH and route).
6. **Medical and Toxicological Relevance**
   Therapeutically used in ADHD and narcolepsy at low doses.
   Recreational or high-dose use causes acute toxicity (hypertension, hyperthermia, agitation) and long-term neurodegeneration.

CONCLUSION

Methamphetamine is a potent synthetic central nervous system stimulant belonging to the amphetamine class of phenethylamines. Chemically characterized by its phenyl ring, methylated amine group, and chiral structure, it exists primarily as the dextro isomer, which exhibits strong psychoactive effects. While it has limited medical applications—notably in the treatment of ADHD and narcolepsy—its high abuse potential has led to widespread recreational use, posing significant public health concerns.

Pharmacologically, methamphetamine acts by enhancing the release and inhibiting the reuptake of monoamine neurotransmitters, particularly dopamine, norepinephrine, and serotonin, producing stimulation, euphoria, and increased alertness. Chronic use, however, results in neurotoxicity, cognitive deficits, cardiovascular strain, and addiction. Its physical and chemical properties, including solubility, crystallinity, and stereochemistry, play a critical role in both its pharmacological activity and forensic identification.

Historically, methamphetamine has seen medical and military applications, but its modern relevance is largely dominated by its abuse, neurotoxic effects, and stringent legal control. Understanding its chemical structure, pharmacology, and controlled production is crucial for both clinical use and public health interventions, as well as for forensic and regulatory purposes.

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