Central nervous system stimulants: basic pharmacology and relevance to anaesthesia and critical care

Ryan Campbell
Simon P Young

Learning objectives

After reading this article, you should be able to:

- classify CNS stimulants into three groups
- explain the mechanism of action of common CNS stimulants
- appreciate the relevance of sympathomimetics in anaesthesia and critical care, and the potential dangerous interactions that can occur between drugs of abuse and agents used in the perioperative setting

Abstract

Central nervous system (CNS) stimulants are common in clinical practice, and have a high potential for abuse. The CNS stimulants can be classified as analeptic stimulants, psychomotor stimulants, or methylxanthines. Doxapram activates peripheral chemoreceptors and central respiratory centres in a dose-dependent manner. Psychomotor stimulants (e.g. cocaine and amfetamines) increase sympathetic nervous system activity. Competition for various metabolic and transport processes can lead to dangerous drug interactions. Sympathomimesis in the perioperative period may result in haemodynamic instability, cardiac dysrhythmias, and myocardial ischaemia. Therapeutic methylxanthines are used mainly to stimulate respiratory centres.

Keywords Amfetamine; analeptic; methylxanthine; stimulant; sympathomimetic

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Introduction

Central nervous system (CNS) stimulants are common drugs of abuse, but still have legitimate uses in clinical practice. Anaesthetists and intensivists may be involved in managing patients with acute intoxication or chronic dependence relating to CNS stimulant usage, or may have to consider using stimulants in the perioperative and critical care setting. An understanding of the pharmacology and adverse effects of this group of drugs allows for safer patient management. The CNS stimulants can be broadly classified as follows:

- analeptic stimulants
- psychomotor stimulants
- methylxanthines

Analeptic stimulants

The term 'analeptic stimulants' historically describes a group of drugs used to lighten narcosis, stimulate respiratory centres and restore depressed central nervous system function. Analeptics can be subcategorized as convulsants (strychnine, picrotoxin and bicuculline) or respiratory stimulants (doxapram, nikethamide and pentylenetetrazole).

Although highly toxic, the plant alkaloid strychnine was used in medicinal tonics until the early 20th century. Strychnine causes CNS excitation by competitively antagonizing the inhibitory neurotransmitter glycine. In low doses patients experience heightened awareness, restlessness and tachypnoea. Higher doses of strychnine produce exaggerated motor responses to visual, auditory and tactile stimulation, tonic extension, generalized convulsions, and respiratory arrest. No longer used in clinical practice, strychnine is available as a rodenticide — intoxication can be seen in cases of deliberate self-harm or accidental ingestion (it is used as an adulterant in illicit drugs such as heroin). Other notable convulsants include picrotoxin and bicuculline which antagonize the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Neither are commonly accessible.

Few respiratory stimulants remain in clinical use due to concerns over margins of safety. Doxapram is a dose-dependent respiratory stimulant which is believed to stimulate peripheral carotid or aortic body chemoreceptors at low doses through pH sensitive TASK (TWIK-related acid sensitive K^+) channels, and central respiratory centres in the medulla at higher doses. The resulting increased minute volume is predominantly a result of increasing tidal volumes rather than respiratory rate. Boluses of doxapram (1 mg kg^{-1}, but not recommended in children) can be used to encourage spontaneous ventilation in patients with respiratory depression following general anaesthesia. Continuous infusions of doxapram (90–240 mg h^{-1}) can be used in acute respiratory insufficiency, particularly in exacerbations of chronic obstructive pulmonary disease; this role has diminished since the adoption of non-invasive ventilation.

Psychomotor stimulants

This group includes sympathomimetic amides, such as amfetamines, cocaine, and ephedrine. These adrenergic receptor activating drugs evoke responses mimicking sympathetic nerve stimulation; as such their effects include chronotropy, inotropy, vasoconstriction, bronchodilation, respiratory stimulation, increase in wakefulness and psychomotor activity, muscle tremor, and appetite suppression.

Sympathomimetics can be subclassified based on their site of the action: direct acting (acting at the post-synaptic adrenoreceptors), indirect acting, or dual acting (working through both direct and

Ryan Campbell *MBChB FCARCSI is an ST7 in Anaesthesia and Clinical Fellow in Neuroanaesthesia at the Institute of Neurological Sciences, Glasgow, UK. Conflict of interest: none declared.*

Simon P Young *BSc MBChB FRCA EDIC FFICM is a Consultant Neuroanaesthetist at the Institute of Neurological Sciences and the Royal Hospital for Sick Children, Glasgow, UK. Conflict of interest: none declared.*

indirect mechanisms). The effects of sympathomimetic drugs can be predicted through knowledge of the physiology of sympathetic nervous system.

Indirect acting sympathomimetics can work through several mechanisms (see Figure 1):

- by preventing re-uptake of monoamines
  - Via inhibition of Uptake-1, a high-affinity low-capacity transporter system which is responsible for neuronal uptake of monoamines into nerve terminals. Uptake-1 has a relative selectivity for noradrenaline, and is associated with the norepinephrine transporter (NET). Drugs inhibiting Uptake-1 include cocaine and tricyclic antidepressants.
  - Via inhibition of Uptake-2, a low-affinity high-capacity system linked with extraneuronal uptake of catecholamines. Uptake-2 is inhibited by corticosteroids and β-haloalkylamines (e.g. phenoxybenzamine).
- by inhibiting transport into intracellular storage vesicles
  - Via inhibiting vesicular monoamine transporter-2 (VMAT-2), so increasing cytosolic concentrations of monoamines. VMAT inhibitors include amfetamines, methamfetamine, MDMA, and reserpine.
- by promoting displacement of catecholamines from intracellular storage vesicles
- by preventing metabolic degradation of catecholamines
  - Via inhibition of monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT).

Monoamine oxidase inhibitors (MAOI) and COMT inhibitors are not traditionally considered to be CNS stimulants.

Amfetamines (International non-proprietary name for amphetamines)

Amfetamines are a group of synthetic phenylethylamine derivatives, structurally similar to noradrenaline and dopamine (Figure 2). Substitutions to the basic chemical structure of the parent compound amfetamine can produce multiple amfetamine analogues, including 3,4-methylenedioxy-N-methylamfetamine (MDMA, 'ecstasy'), methamfetamine ('crystal meth'), and methylphenidate. These substitutions can result in amfetamine analogues having distinctly different pharmacological effects including altered receptor affinity profiles, blood–brain barrier penetration, and anorexic effect. Subtle structural differences from catecholamines mean that amfetamines do not get

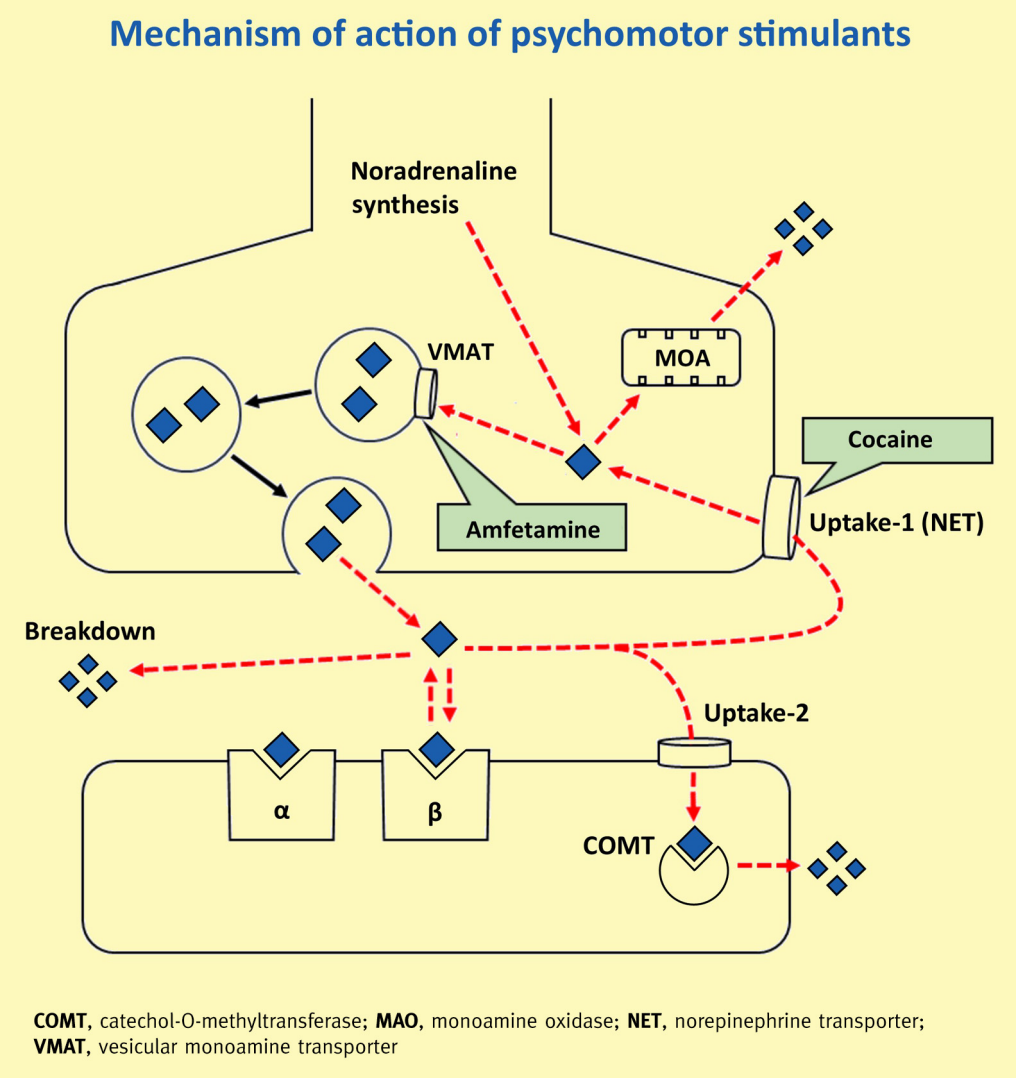

Figure 1