A study in grey

Effects of cocaine and nicotine on the organism in the novel

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Introduction


Sherlock Holmes.

Throughout their best-selling novels, Sherlock Holmes and Hercules Poirot confront all kinds of evildoers, but there is nothing quite as evil as a villain that murders from a distance, neatly, with a poison. Cocaine and nicotine are sympathomimetic drugs that can be used as such, but in lower doses they can light the flame of addiction and even serve as a remedy, as was already stated by Paracels in the 16th century. The double goal of this review consists in acknowledging their effects on the organism and toxicity, and stating whether Sir Arthur Conan Doyle and Agatha Christie described their effects correctly.


Hercules Poirot.

Materials and Methods

- In all the books written by both authors in digital format, a search of the keywords *cocaine*, *dope*, *nicotine*, *tobacco*, *pipe* and *cigarette* was done in order to read the stories and grasp the context in which they were being used.
- In Pubmed Database and renowned pharmacological books, a search of data related to cocaine and nicotine pharmacology, activation of peripheral nervous system, action in central nervous system, mechanism of addiction and toxicity was done. All relevant data was selected, read and summarized.
- Having read the two groups of literature, a process of comparing and contrasting the scientific data with the style of the authors was carried out.

Cocaine's impact on the organism

Cocaine is a non-selective inhibitor of monoamine transporters in synapses (Figure 1). The main routes of administration are inhalation and intravenous so it can rapidly be absorbed into the bloodstream. Its half-life oscillates between 0.7 and 1.5 hours and it is primarily metabolised in the liver, being it and its inactive derivatives excreted in urine.

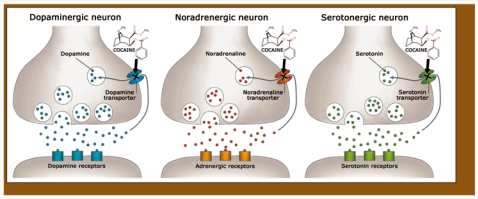
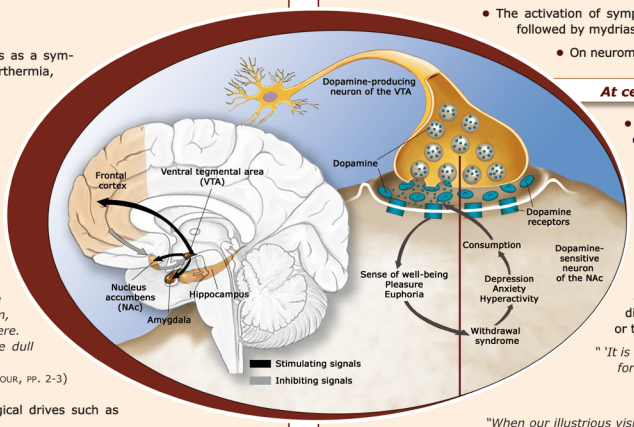


Figure 1. *Schematic representation of axon terminals of monoaminergic neurons affected by cocaine. Infographic by author.*

Figure 2. *Brain reward pathway (BRP) and influence of dopamine signalling on the mood. The BRP consists of the dopaminergic neurons of the Ventral Tegmental Area (VTA) and their projections to the nucleus accumbens (NAc), to the prefrontal cortex and to regions of the amygdala and hippocampus. Infographic by author.*



At peripheral level

- Through the inhibition of noradrenaline transporters, cocaine acts as a sympathomimetic drug that triggers blood vessels contraction, hyperthermia, tachycardia and hypertension, twitching, mydriasis, etc.

> " *'All the women showed signs of dope —nerves, irritability— twitching, pupils of eyes dilated, etcetera' ".*
> (The Capture of Cerberus, from The Labours of Hercules, p. 392)

At central level

- Cocaine inhibits the reuptake of dopamine in the nucleus accumbens (NAc) of the brain reward pathway (BRP) (Figure 2). Low doses of cocaine make the user feel euphoric, energetic and alert.

> " *'I find [cocaine], however, so transcendently stimulating and clarifying to the mind that its secondary action is a matter of small moment. [...] My mind rebels at stagnation. Give me problems, give me work, give me the most abstruse cryptogram, or the most intricate analysis, and I am in my own proper atmosphere. I can dispense then with artificial stimulants. But I abhor the dull routine of existence. I crave for mental exaltation' ".*
> (The Sign of Four, pp. 2-3)

- Cocaine also inhibits serotonin transporters, weakening physiological drives such as appetite and sleep.

> " *'Because the faculties become refined when you starve them. Why, surely, as a doctor, my dear Watson, you must admit that what your digestion gains in the way of blood supply is so much lost to the brain' ".*
> (The adventure of the Mazarin Stone, from The Casebook of Sherlock Holmes, p. 73)

- Higher doses may cause hallucinations and psychoses, and even violent behaviour and suicidal or homicidal thinking.

> " *'Cocaine peps you up and you feel you can do twice as much as you usually do. Take too much of it and you get violent mental excitement, delusions and delirium' ".*
>
> " *'I've got insects crawling all over me... I have. I swear I have. I'm going mad...' ".*
> (The Horse of Diomedes, from The Labours of Hercules, pp. 265-269)

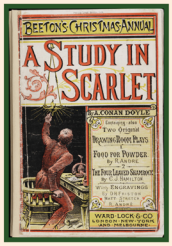


Figure 3. *Front cover of Beeton's Christmas Annual in 1887 where* A Study in Scarlet *was featured. (From The Lilly Library, Indiana University, Bloomington, IN, USA).*

- When the pleasurable effects of cocaine die away, the consumer feels the so-called withdrawal syndrome, characterized by depression, anxiety, nervousness, etc. It is believed that it befalls when neurotransmitters are taken back into the axon terminal, and that the desire to consume that comes afterwards responds to the need for them to flood the BRP.

> " *'My nerves are all to pieces! [...] It will steady me. Pull me together' ".*
> (Death in the Clouds, pp. 19, 238)

- Cocaine causes addiction by its own mechanism of action in the BRP. Addiction is defined as a chronic and relapsing disorder which entails compulsion to take the drug, inability to ponder the consequences and emergence of a negative emotional state when access to the drug is impeded. Addiction to cocaine not only stems from the neuroadaptations caused by the drug, but also from social influences and genetic and epigenetic factors.

> " *'Now I knew that under ordinary conditions he no longer craved for this artificial stimulus; but I was well aware that the fiend was not dead, but sleeping; and I have known that the sleep was a light one and the waking near in periods of idleness' ".*
> (The Adventure of the Missing Three-Quarter, from The Return of Sherlock Holmes, pp. 300-301)

As a poison

- It is estimated that cocaine's minimum lethal dose is 17 mg/kg. This overdose can lead to seizures, coma, myocardial infarction, cardiopulmonary arrest and cerebral haemorrhage.

> " *'I suspect that [Coco's death] was an accident cleverly engineered by Davidson. She was furiously angry with Cronshaw, first for his reproaches, and secondly for taking her cocaine from her. Davidson supplied her with more, and probably suggested her augmenting the dose' ".*
> (The Affair at the Victory Ball, from Poirot's Early Cases, p. 24)
>
> " *'Mademoiselle Nick is dangerously ill. Cocaine poisoning' ".*
>
> *"Nick was sitting up in bed. The pupils of her eyes were widely dilated. She looked feverish and her hands kept twitching violently".*
> (Peril at End House, pp. 215, 219)

Nicotine's impact on the organism

Nicotine acts agonistically on nicotinic cholinergic receptors (nAChRs) (Figure 4). It is usually conveyed into the lungs by the smoke particles from a cigarette, but it can also be ingested. Then it is absorbed into the bloodstream and distributed to different tissues, where it will bind to nAChRs. Its plasma half-life is, on average, about 2 hours and, although nicotine is mainly metabolised in the liver to cotinine, both of them can be eliminated in urine.

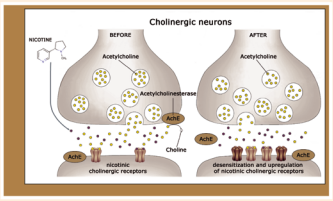


Figure 4. *Schematic representation of nicotine action in post-synaptic nicotinic cholinergic receptors. Infographic by author.*

At peripheral level

- The sympathomimetic action of nicotine causes tachycardia, increased stroke volume and hypertension due to blood vessels contraction. Additionally, it triggers release of catecholamines from the adrenal medulla which heightens all of the aforementioned (Figure 5).
- The activation of sympathetic and parasympathetic nervous system results in miosis followed by mydriasis and bronchospasm.
- On neuromuscular junctions, binding to nAChRs provokes muscle contraction.

At central level

- Nicotine binds to nicotinic receptors in the dopaminergic neurons of the Ventral Tegmental Area (VTA), which release dopamine in the NAc, making the individual feel a sense of well-being.
- nAChRs can desensitize to the action of the ligand, being no longer responsive for a period of time. However, the homeostatic response of the organism is to upregulate the number of nicotinic receptors (Figure 4). Maintaining those receptors unresponsive, as well as preserving dopamine molecules overflowing the NAc, prevents emergence of withdrawal syndrome.
- Nicotine enhances certain aspects of cognitive function, such as memory and attention, and this fact could either be due to a direct effect of nicotine on the hippocampus and prefrontal cortex or to the relief of its own abstinence syndrome.

> " *'It is quite a three-pipe problem, and I beg that you won't speak to me for fifty minutes' ".*
> (The Adventure of the Red-Headed League, from The Adventures of Sherlock Holmes, p. 43)
>
> *"When our illustrious visitors had departed Holmes lit his pipe in silence and sat for some time lost in the deepest thought".*
> (The Adventure of the Second Stain, from The Return of Sherlock Holmes, p. 369)

As a poison

- It is assumed that nicotine lethal dose is 0.86 mg/kg, so intoxication is more common after ingestion of nicotine than smoking. In such cases, it produces fasciculations and seizures and muscarinic symptoms such as vomits and salivation. Death follows shortly, due to neuromuscular blockade which leads to respiratory muscle paralysis or cardiovascular collapse.

> *"Mr Babbington had risen to his feet and was swaying to and fro. His face was convulsed [...] 'Look,' said Egg's voice. 'Mr Babbington is ill' ".*
>
> " *'Mr Babbington was taken ill a very few moments after entering the room and just after drinking his cocktail. Now, I did happen to notice that he made a wry face when drinking' ".*
> (Three Act Tragedy, pp. 34, 41)

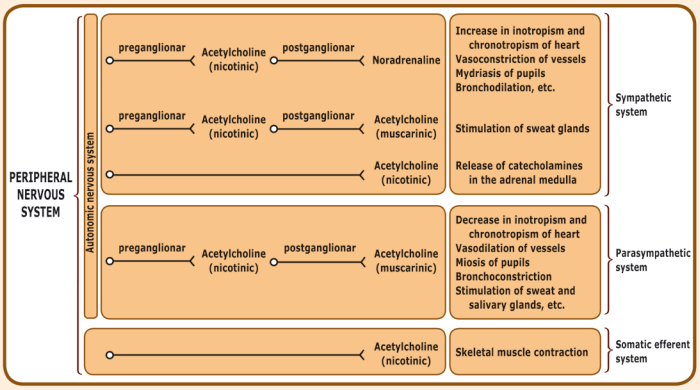


Figure 5. *Components and action of the Peripheral Nervous System. (Modified from Hall, J. E. & Guyton, A. C.* Guyton and Hall textbook of medical physiology, *Elsevier Saunders, 2011).*

Concluding remarks

Although roughly 30 years stand between Doyle and Christie, both shared a medical background and a passion for intrigue and crime novels. With the examples provided, it is tangible that Christie described the effects of cocaine and nicotine more accurately than Doyle did and that she did not ignore some of the unwanted effects that spring from their consumption; however, it could be that Doyle deliberately wanted to create a detective who was less vulnerable to the human condition, or that Christie preferred to be less fictional in her descriptions. What is true is that both detectives and their worlds were marvellously written, and that such page-turner classics will always live on.

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