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Smoking, Synapses, and Systems, Oh My! Nicotine's Whole-Body Effect

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Part I – Neurobiological Effects of Nicotine

Sarah Bennett sat near the window of her advanced placement tenth-grade biology class, twirling her pencil as her teacher pulled up a slide for the newest learning module, "The Impact of Nicotine on the Brain." Sarah had learned about nicotine and the dangers of cigarettes in school, as well as through warning posters at her doctor's office, so she really didn't think there was anything new she could learn about the topic. However, the first slide piqued her interest as she glanced up and saw it was on the neurobiological effects of nicotine.

Her teacher began by explaining that nicotine ($C_{10}H_{14}N_2$), a naturally occurring organic alkaloid, is one of the most frequently used and abused drugs in the world aside from caffeine. Classified as a stimulant, nicotine is found primarily in tobacco plants (*Nicotinia tabacum*) and is the primary psychoactive component of tobacco. Indigenous people in the Americas cultivated and used tobacco long before European contact, often for medicinal, ceremonial, or social purposes (Mark, 2021). With the arrival of European explorers, tobacco rapidly spread across the globe in the form of cigars, cigarettes, and snuff (Mishra & Mishra, 2013). More recently, it has become easily accessible for young adults via electronic cigarettes and vape pens.

Nicotine's powerful addictive potential depends on its ability to bind to nicotinic acetylcholine receptors (nAChRs). These ionotropic ligand-gated ion channel receptors are critical for rapid synaptic activation and responses. Naturally, the nAChRs are activated by acetylcholine (ACh), but the molecular structure of nicotine mimics ACh, allowing it to bind to nAChRs as well. As a result, it can take as little as eight seconds for inhaled nicotine to reach the brain (Sansone et al., 2023).

When nAChRs are activated, the neuron is flooded with cations such as sodium (Na^+) and calcium (Ca^{2+}). This influx alters the cell's electrical activity, leading to depolarization, a shift in charge that makes the cell more positive. With the continuously increasing exposure to nicotine causing ongoing depolarization, the cell's positive threshold is reached, triggering a chain reaction that excites neighboring neurons.

When nicotine binds to nAChRs in the ventral tegmental area (VTA), it stimulates dopaminergic neurons, leading to increased dopamine release in the nucleus accumbens (NAcc). The pathway in the brain from the VTA to the NAcc is known as the mesolimbic pathway. This pathway is central to reward and reinforcement (O'Dell, 2009). The pathway from the VTA to the prefrontal cortex (PFCx) is known as the mesocortical pathway, which influences executive function, decision making, and impulse control (Feltenstein et al., 2021). Together these interconnected circuits form the mesocorticolimbic system, the core of the brain's reward circuitry involved in addiction as seen in Figure 1.

The surge of dopamine after binding nicotine creates feelings of pleasure and reinforcement, which are central to the brain's reward system. Overtime, repeated activation of this pathway strengthens neural circuits associated with reward and motivation, making nicotine use highly reinforcing and difficult to quit (Feltenstein et al., 2021).

This activation also influences the release of inhibitory neurotransmitters like gamma-aminobutyric acid (GABA) and excitatory ones like glutamate, creating a complex balance of neural activity. Nicotine can activate GABAergic interneurons, which would normally inhibit dopamine neurons. However, nAChRs on GABA neurons can desensitize quickly, reducing GABA release over time and thus removing the inhibitory brake, allowing dopamine neurons to fire more freely. The combination of increased glutamate excitation and reduced GABA inhibition creates a strong dopaminergic response, and this imbalance is a key mechanism behind nicotine's reinforcing and addictive properties (D'Souza & Markou, 2013).

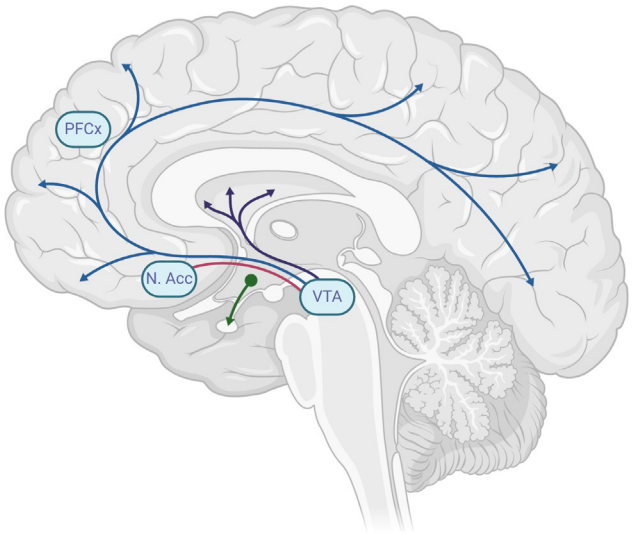

Figure 1. Depiction of the mesocorticolimbic system. The VTA, N. Acc, and PFCx are highlighted.

Nicotine has a half-life of roughly two hours, so it is quickly eliminated from the body after each use (Sansone et al., 2023). The rapid clearance contributes to withdrawal symptoms that can start as soon as six to twelve hours after smoking cessation, peak within one to three days, and gradually subside over a week to a month (Nicotine Withdrawal, 2024). During withdrawal, disrupted neurotransmitter activity often results in sleep disturbances and dysregulation of normal sleep-wake cycles, as the brain's chemistry adjusts to the absence of nicotine after exposure.

The idea that a plant compound could slip into the brain's communication system and alter it, fascinated Sarah. She felt a rush of awe at how complex and delicate the human mind was, and how something as small as a molecule could shift thoughts, moods, and even habits. Her teacher continued to teach about the paradox of nicotine.

Questions

1. Nicotine exerts its psychoactive effects by mimicking the molecular structure of which naturally occurring neurotransmitter, allowing it to bind to its receptors?

2. Describe the precise molecular events that happen when nicotine binds to the nAChR.

3. Which brain regions are identified as the primary components of the reward circuitry targeted by nicotine? Evaluate how alterations in prefrontal cortical function due to nicotine exposure may impair decision-making and contribute to continued nicotine use despite the negative consequences.

4. Design an experimental study to investigate how chronic nicotine exposure alters synaptic plasticity in the mesocorticolimbic pathway. Include hypotheses, methods, and expected outcomes.

Part II – The Paradox of Nicotine Addiction

The effects of smoking are somewhat paradoxical, where users describe a "calming" psychological experience, but have a counterintuitive physiological experience. Throughout the night, a typical smoker can experience numerous cravings leading to sleep disruptions. Smokers are known to have cigarettes prior to going to bed, for withdrawal and habitual reasons, but then experience trouble falling asleep, staying asleep, and can even experience sleep apnea. Insomnia is a frequent diagnosis among smokers, due to the release of the adrenaline neurotransmitters, epinephrine (Epi) and norepinephrine (NE), before sleep. Nicotine sleep disturbances are entirely dependent on the quantity and frequency of nicotine intake, with symptoms becoming exacerbated through increased consumption (Branstetter et al., 2016).

An increase in nicotine consumption can lead to addiction and the level of addiction can be calculated by looking at the "time to first cigarette" (TTFC). The sooner an individual reaches for a cigarette after waking, the more severe the addiction (Branstetter et al., 2020). This urgency is due to the user subconsciously titrating their nicotine levels to maintain a consistent concentration within their bloodstream, which can lead to routine excused breaks from society or stressful situations. The act of smoking not only becomes a neurological craving but starts to slowly incorporate more psychological and behavioral traits as well. Smokers tend to develop an oral fixation, after being accustomed to having a cigarette in their mouth. The "breaks from society" begin to enforce the "calming" effect of cigarettes as they are given a chance to escape overstimulating environments and stressful situations. This self-removal from one group can open doors to other similarly routined individuals to share stories with, providing an opportunity to create new friendships.

As the teacher explained how nicotine could create dependency and hijack the reward circuits in the brain, Sarah felt a tug of contradiction. She wondered, *If it's so dangerous, why do so many people still use it? If it's just one time, it can't really hurt, right?* And in that moment, her curiosity crossed into temptation, a dangerous step that would change far more than she expected.

Question

5. The effects of smoking are described as paradoxical: users report "calming" psychological experience, despite the opposite physiological effects. Analyze this paradox integrating the release of NE and Epi with the observed psychological and behavioral benefits.

Part III – Sarah's Superfluous Smoking

Sarah had been smoking since sixteen, ever since experimenting after school that fateful day. Over time, she felt less stressed and was even accepted into a new friend group because of their shared "interests." It was not until her early thirties that she noticed her shortness of breath and consistently poor quality of sleep. She figured it was due to the late hours and high stress environment of her job as a restaurant manager. Over time, her smoking habit got worse, and by fifty-two years of age, she was smoking 15–20 cigarettes (roughly a pack) a day. Her TTFC was 15 minutes, followed quickly by two cups of black coffee (around 200 mg of caffeine) to start her morning. She often worked weekends, starting at 2 p.m. and finishing around 11 p.m. One of her promotions required her to close the restaurant every other week, which often meant getting home by 1 a.m. or later.

Sarah did not put a priority on caring for her body, and overtime she found herself struggling to breathe. She always had some difficulty when doing physical activities, but now she was starting to struggle for air even at rest, and she made a slight wheezing sound when she exhaled. The long work hours took a toll on her body; the body that could once easily get out of bed, now struggled to move. She couldn't figure out why she was so tired, but when she checked her sleep time on her smart watch she understood. Her time in bed averaged three hours, between 3 a.m. and 6 a.m. She averaged ten awakenings per night during the three-hour sleep time. Overall, her sleep quality rating was dangerously low.

Finding herself with a rare day off, Sarah decided to visit the doctor to see if she could get some help with her sleep. After discussing her medical history with the doctor, she underwent extensive medical testing. Below are the doctor's notes.

Chief Complaint

The patient complains of mild exertional dyspnea and mild shortness of breath at rest, with increased difficulty sleeping at night. No history of asthma and no alcohol or illicit drug use.

Physical Examination

General: alert, oriented, BMI slightly below normal.
Respiratory: mild barrel chest, diminished breath sounds bilaterally, prolonged expiratory phase.
Cardiac: normal heart sounds, no peripheral edema, distant heart sounds.
Skin: clubbing without signs of cyanosis. Mild discoloration on fingertips.

Vital Signs

BP: 128/78 mmHg (Normal: ~120/80 mmHg)
HR: 88 bpm (Normal: 60–100 bpm)
RR 18 breaths/min (Normal: 12–20 breaths/min)
SpO_2: 94% on room air (Normal: 95–100%)

Pulmonary Function Test

FEV_1: 65% predicted (Normal ≥ 80% predicted)
FVC: 72% predicted (Normal ≥ 80% predicted)
FEV_1/FVC ratio: 0.68 (Normal ≥ 0.70)

Chest X-Ray

Hyperinflated lungs, flattened diaphragm (Normal: clear lung fields, normal diaphragm contour).

Arterial Blood Gas

$PaCO_2$: 48 mmHg (Normal: 35–45 mmHg)
PaO_2: 72 mm Hg (Normal: 80–100 mmHg)
Mild hypercapnia

Question

6. Based on the doctor's notes, what respiratory disease do you think Sarah has? Explain how you reached your conclusion.

Part IV – Diagnosis

Sarah was diagnosed with chronic emphysema and warned by her physician of the potential risks. Her doctor explained that her condition falls under the chronic obstructive pulmonary disorder (COPD) umbrella. Patients with this type of pulmonary disease present with damaged, enlarged, and inflamed alveoli (Washko et al., 2011). The alveoli are the small balloon-like portions of the lungs that allow gas exchange. When this part of the body is inflamed, the muscles that aid in breathing and the mechanisms that control them work differently, most notably when trying to sleep (Krachman et al., 2008). These changes can sometimes affect breathing and lead to sleep problems.

"How long have your symptoms been occurring?" the doctor asked.

Sarah sat at the edge of the exam table and looked down at her hands. She was embarrassed to admit how long she had ignored her health and the warning signs. Her doctor pointed out her hands, which had enlarged and rounded nails known as clubbing, and her fingertips had yellowish-brown discoloration on her thumb, index, and middle fingers known as "smoking fingertips" (John et al., 2013).

"It's been years," she said feeling defeated and ashamed. "I can't believe I let it get this bad."

Her doctor grabbed her chest X-ray and held it out. The image showed lungs that looked hollow and stretched thin. "Unfortunately, this is a chronic condition. While it won't go away, we can try to manage it through lifestyle changes and proper medications."

Sarah was in shock. "What does that mean?"

"The most important step now is to quit smoking immediately," he stated. "This will slow the progression of your emphysema and improve your lung function over time. You'll start using an inhaler every day to keep your airways open, and I'm going to refer you to a pulmonologist who will set you up with a pulmonary rehabilitation program. There, they will teach and help you with breathing exercises as well as educate you further on your condition."

She clasped her hands tightly in her lap and she could feel the tears pooling in her eyes. She had come in expecting a check-up and some medication, maybe a lecture or two, but she felt like the wind had been knocked out of her already winded chest. Staring at the X-ray, she thought of how cigarettes had been her constant companion since she was young. Now they were the source of her demise. She felt a surge of heat flood through her body, not just of fear but of regret and self loathing. Quit smoking, inhaler, specialists, rehab…change.

As she left the doctor's office with a prescription in hand, she habitually went for a cigarette and caught herself. She found a lollipop her daughter had left in her bag and quickly unwrapped the covering and put it in her mouth. She thought to herself, *This isn't the end, it's the beginning of something harder…something better.* She realized her life would be completely different now, her morning routine without a cigarette, her evenings without her smoke breaks, her guaranteed fifteen minutes away from stress and people. She knew quitting would be difficult and daunting, but she was willing to put in the hard work.

Questions

7. What physical sign on her hands did the doctor point out as evidence of her long-term smoking habit?

8. Smokers often experience insomnia and sleep disturbances. Propose a link between Sarah's respiratory disorder and her sleep.

Part V – Hurdles and Hope

For the first two weeks, Sarah was highly motivated. She attempted nicotine replacement therapy (NRT) with nicotine gum, patches, and lozenges, and kept herself busy with exercise. However, as stress at work began to build, she started craving her escape, the cigarette breaks. By the third week, she had a minor slip at a party, a single cigarette, but recommitted herself the next day.

During a follow-up appointment, Sarah sat across from her doctor, who gently explained the reality of quitting smoking. "Most people relapse within the first month, especially when life throws a high-stress situation towards them." The words lingered in Sarah's mind as she thought of her own stress-filled work schedule. "I recommend we try varenicline along with the nicotine replacement therapies. Studies have shown that by combining medications with the therapies, we may be more successful" (Chang et al., 2015).

Determined to beat the odds, Sarah set a goal to make it to 90 days smoke-free. For the first few weeks, she felt confident, using daily walks, nicotine patches, and nicotine gum to manage cravings. But by the sixth week, her workload doubled and the pressure became overwhelming; however, with each passing week, Sarah noticed a gradual improvement in her quality and quantity of sleep, although each day felt like a battle against old habits. She knew quitting would be brutal, but she was willing to put in the hard work. Sarah would fight for every breath, every day, because this was her chance to take back what smoking had stolen.

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