Effects of Psychoactive Drugs on Sleep Quality and Pain Sensitivity

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Abstract

Sleep is an essential part of every person's life. Many drugs initially prescribed and then abused for pain management, such as nicotine, cocaine, and opioids, can have lasting effects on sleep modulation, a relationship that we explore in this review. We specifically examine nicotine and caffeine's effects on sleep and pain. In addition, the most commonly used stimulant, caffeine, which affects the adenosine A2A receptor, can also have lasting impacts on pain. Previous research by Foo et al., (2003), Chen et al., (2013), and De Biasi et al., (2011) has demonstrated that these drugs alter many neurochemical and neurobiological systems in the brain, such as dopaminergic pathways, adenosine receptors, and the sympathetic nervous system. Nicotine decreases pain through the release of dopamine short-term, but long-term use can exacerbate pain. Nicotine also alters sleep quality because it reduces REM and wave sleep through the prefrontal cortex, leading to a later onset of sleep and increased daytime sleepiness. Caffeine can aid in pain when used in moderation and sometimes with other pain-relieving drugs, but when used in excess can lead to headaches and more pain. Caffeine alters sleep by reducing total sleep time and altering the 24-hour circadian rhythm. Therefore, these drugs, commonly used to aid pain, may also worsen pain, doing the opposite of their intended effects.

1 Introduction

Sleep deprivation is a rising problem in the US, affecting social and economic spheres like worker productivity and awakeness. According to The Sleep Foundation, Adults 18+ are recommended to sleep 7-9 hours every night, with 35 percent of Americans getting less than this value. This problem is even more prominent among adolescents, with only 3 percent of adolescents in the US getting the recommended 8-10 hours of sleep per night. The problem is not improving; since 1985, the number of adults getting less than six hours of sleep has increased by 31 percent. The US economy loses over 410 billion dollars

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annually due to sleep deprivation, which is 1.78 percent of the US's GDP. The increased use of addictive drugs exacerbates these social and economic issues.

Many drugs of abuse are becoming more prominent, with nicotine use increasing by 33.8 percent from 2012 to 2019 among US high school students[1]; Americans drink coffee every day more than any other beverage, including tap water. A National Survey on Drug Use and Health released that one in 20 people surveyed reported using cocaine. Opioid prescriptions are over 150 million annually in the US. Combined, one can infer that these drugs that modulate pain are becoming more prominent in the US. Cocaine, opioids, and caffeine are used for their rewarding effects and for reducing their effects on pain perception. However, how pain-modulated drugs of abuse alter sleep has not been explored. This review examines the lasting effects of these drugs on pain and sleep and the underlying neurobiological mechanisms that cause these relationships.

1.1 Brain Regions that Modulate Sleep

There are a variety of brain regions that modulate the circadian rhythm and the body's sleep/wake cycle. Two main types of sleep are essential to understanding the body's sleep cycle: REM and NREM sleep. REM sleep refers to rapid eye

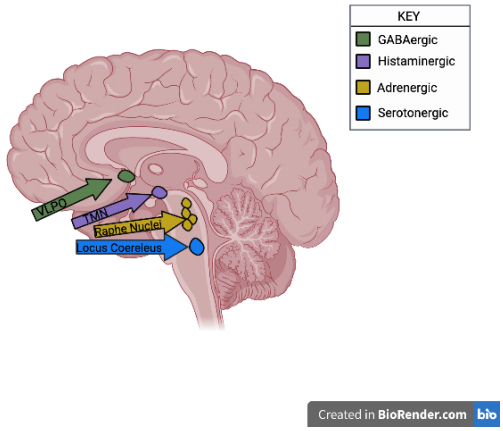


Figure 1: Sleep regions of the brain

movement sleep, often the stage of sleep in which dreams occur. NREM sleep is nonrapid eye movement sleep, which often comprises slow-wave and deep sleep. Both types of sleep are essential for growth, development, and many other functions related to sleep. Some neurotransmitters that are key to understanding the sleep/pain relationship are Serotonin, also known as the 'happy hormone,' which also serves a variety of other metabolic effects. Histamine is a neurotransmitter that is often associated with inflammation and allergy response. In

[1] Jackson, S. E., Brown, J. Jarvis, M. J. Dependence on nicotine in US high school students in the context of changing patterns of tobacco product use. Addiction 116, 1859–1870 (2021).

addition to the various brain regions, various neurotransmitters correspond with those regions. For example, serotonergic neurons in the raphe nuclei, including the Ventromedial Medulla (VMM), adrenergic neurons in the locus coeruleus, and histaminergic neurons in the tuberomammillary nucleus have been shown to have high activity during wake states, lower activity during NREM sleep and almost no activity during REM sleep. Therefore, these brain regions are related to the brain's 24-hour sleep/wake cycle. Another brain region essential to sleep modulation is the Ventrolateral Preoptic Area (VLPO), whose projections affect Gamma-Aminobutyric Acid (GABA) compounds. GABA is a neurotransmitter highly related to sleep modulation as its inhibitory actions are well established, and most current treatments to sleep disorders target GABA neurons. The adrenergic neuron activity antagonizes the GABA release from the VLPO neurons during wake, inhibiting the release. This negative feedback loop ensures that we are awake during the state.

Neuropeptides are different from neurotransmitters as they are larger molecules and have effects that last hours, while neurotransmitters often have effects that last seconds. In addition to neurotransmitters that modulate sleep, various neuropeptides are related to brain regions that modulate sleep. One well-known peptide that serves multiple purposes in the brain and regulates the sleep/wake cycle is Hypocretin (Orexin). Some of these purposes of Orexin are homeostasis, cognition, and mood. Hypocretin also has an allosteric (regulatory) relationship with the neurotransmitter Melatonin, made in the pineal gland of the midbrain that induces sleep. During the day, Hypocretin excites Melatonin, increasing sleep pressure, whereas, during sleep, Melatonin inhibits the Hyprocretin neurons[2], demonstrating a clear relationship in the sleep/wake cycle. Other regions of the brain that modulate sleep are the basal forebrain, which contains cholinergic neurons that are wake and REM active, as well as the lateral hypothalamus, which contains melatonin-concentrating hormones that are most active during REM sleep. Another Neuropeptide of interest is Galanin: a neuropeptide found within the GABA neurons and can decrease arousal. Many animal studies have found that REM sleep deprivation has led to the introduction of Galanin receptors.

Norepinephrine, primarily synthesized in the Locus Coeruleus, is a method of encoded stress. Stress is a potent regulator of sleep. Studies show that different forms of stress alter sleep cycles differently. For example, while REM sleep is critical, excessive amounts may decrease humans' vital NREM sleep for physiological function. Short stress decreases REM sleep, while repeated stress increases REM sleep, possibly leading to other effects.

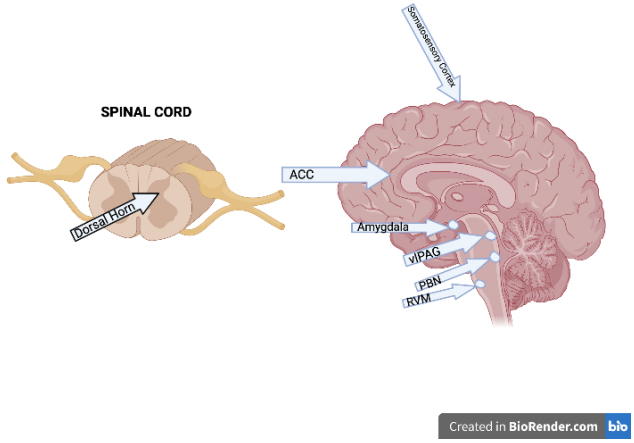
Another region that's activity depends on the sleep-wake state is the Ventromedial Medulla (VMM, located in the midbrain, which relays pain information between the brain and the spinal cord. There are two types of nonserotonergic neurons in the VMM: ON neurons, which are activated by heat stimulation and inhibited by morphine and facilitate pain, and OFF cells, which are the oppo-

[2]Richter, C., Woods, I. G. Schier, A. F. Neuropeptidergic control of sleep and wakefulness. Annu. Rev. Neurosci. 37, 503–531 (2014).

site and inhibit pain. ON cells are more active during wake, while OFF cells are more active during NREM and REM sleep. These neurons are affected by morphine and other opioids, showing the pathway of pain inhibiting from these addictive opioids. There is no evidence that these ON/OFF cells are affected by cocaine, nicotine, and caffeine. Present research on VMM activity in rats showed that wake-active rats were much more likely to discharge when moving[3]. The discharge from the VMM implies that its activity increases during wake cycles and movement rather than rest. Although this study only measures a small percentage of VMM neurons, all recorded from male organisms; the data does not represent the whole population.

1.2 Brain Regions that Modulate Pain

In addition to sleep, there are a variety of regions in the brain that modulate pain. Two different tracts modulate pain between the brain and spinal cord, the spinoreticular tract, and the spinothalamic tract. The spinothalamic tract starts in the somatosensory cortex and goes through the periaqueductal grey and the pons to the spinal cord. The spinothalamic tract affects the conscious sensation of pain. The spinoreticular tract comprises the thalamus, the reticular formations of the medulla and pons, and the spinal cord. The spinoreticular tract affects the emotional aspects of pain and the arousal involved with pain. Mu opioid receptors activated by drugs such as morphine and fentanyl decrease



the output of GABA presynaptically and decrease pain modulation.[4] The ventrolateral periaqueductal grey (vlPAG) plays a vital role in the modulation of pain in the brain. The vlPAG, located in the midbrain, has strong antinociceptive(antipain) effects and blocks pain signals from the spinal cord to the brain.

[3]Movement-Related Discharge of Ventromedial Medullary Neurons." Journal of Neurophysiology, vol. 93, no. 2, Feb. 2005, pp. 873–83.

[4]- Fields, H. State-dependent opioid control of pain. Nat. Rev. Neurosci. 5, 565–575 (2004).

The nervous system has two parts, the central and peripheral parts. The central nervous system comprises the brain and the spinal cord, and the peripheral nervous system comprises all the other neurons that span every corner of our body. The spinal cord relays information from the peripheral information about pain to the brain to elicit a physiological response. Many unconscious reflexes solely involve the peripheral nervous system and the spinal cord and often do not require the brain to create an action, another crucial part of our survival related to pain. For all these reasons, the spinal cord has a vital role in pain modulation.

Another critical region of the brain that is involved in the modulation of pain is the Amygdala, a crucial part of our stress 'fight or flight response. The amygdala is a small pea-sized region in our brain that is part of the limbic system; The amygdala plays a key role in the emotional aspects of the pain response. Pain information relayed to the brain goes through the amygdala and elicits an emotional response to pain. When one in sleep deprived, it reduces the amygdala's function and causes it to have heightened responses to negative stimuli, such as pain.

The anterior cingulate cortex (ACC) is another crucial brain region that modulates the pain response. The ACC is located in the frontal lobe of the brain. It is affected by pain from the peripheral nervous system and develops chronic pain after a nerve injury. Sleep deprivation also causes functional deficits within the ventral part of the ACC, causing exacerbated pain[5] .

The Parabrachi nucleus (PBN) is part of the spinothalamic pain tract explained earlier. The PBN is located on the pons of the hindbrain. The PBN helps us identify where the pain is coming from[6]. It receives inhibitory information from the amygdala, which is diminished by chronic pain conditions.

A fundamental structure in descending pain modulation is the rostral ventromedial medulla (RVM) which relays sensory information between the spinal cord and the brain. In a study that analyzed the effects of air-puffed microarousals in rats, rats took longer to wake up during slow-wave sleep cycles than during awake states. This shows how sleep can help reduce pain sensitivity.[7]

1.3 Mechanisms of Action of Concerned Drugs

t is essential to understand the mechanisms of action of the concerned drugs of nicotine and caffeine as it helps one better understand how it affects the brain and the regions it targets.

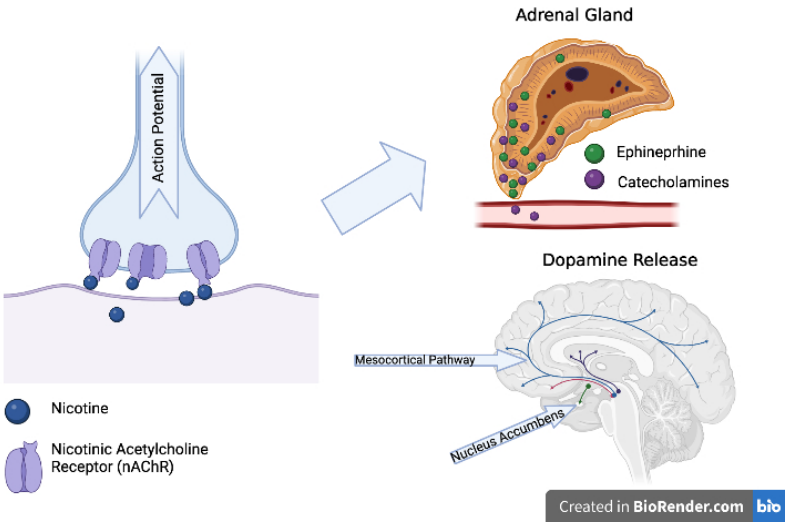
Nicotine's primary effect is on the rewarding dopamine system in the brain by increasing the firing rate and the phasic bursts by midbrain dopamine neurons of

[5]Fuchs, P. N., Peng, Y. B., Boyette-Davis, J. A. Uhelski, M. L. The anterior cingulate cortex and pain processing. Front. Integr. Neurosci. 8, 35 (2014)

[6]Davern, P. J. A role for the lateral parabrachial nucleus in cardiovascular function and fluid homeostasis. Front. Physiol. 0, (2014).

[7]Foo, H., et al. "The Modulatory Effects of Rostral Ventromedial Medulla on Air-Puff Evoked Microarousals in Rats." Behavioural Brain Research, vol. 215, no. 1, Dec. 2010, pp. 156–59

the mesocortical limbic reward system. Nicotine acts on nicotinic acetylcholine receptors within the reward system, specifically the 4 and 2 subunits, often in combination with the 6 subunit. [8]

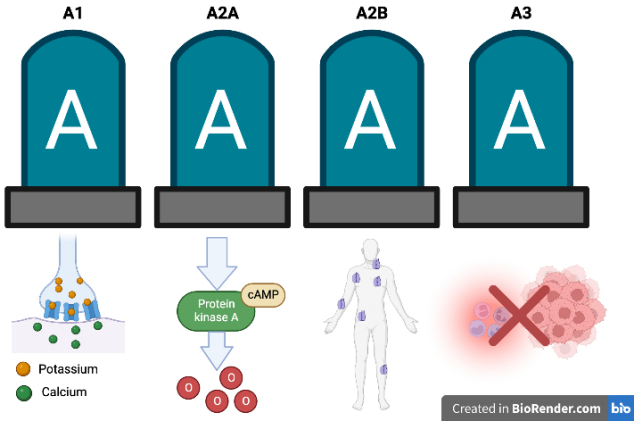


These subunits are taken together to allow nicotine to have powerful effects. In addition, nicotine increases the number of nAChRs in the brain, increasing the craving for the drug and making withdrawal even harder. Another area that nicotine acts on is the nucleus accumbens, increasing dopamine levels there, which is linked to its addictive qualities. In fact, nicotine increases the dopamine released from the ventral tegmental area (VTA) to the mesocortical dopamine pathways. Nicotine also increases norepinephrine activity in the peripheral and sympathetic nervous systems. It also causes the release of catecholamines like epinephrine from the adrenal glands. The brain tends to add more acetylcholine receptors, which leads to withdrawal and craving when nicotine consumption has ended, adding more to its addictive quality. In addition, the withdrawal effects of nicotine impact the epithalamic habenular complex (EHC) of the brain, which regulates mood and fear.

Caffeine is in the Methylxanthine subgroup of drugs and acts as an antagonist to Adenosine receptors. Caffeine has the most significant effect on antagonizing the A2A and A1 subtypes of Adenosine receptors. In addition, caffeine increases dopamine, norepinephrine, and other neurotransmitter levels in the brain. There are four adenosine receptors in the brain, all serving different purposes. The A1 receptor has the highest concentration in the brain at nerve endings, allowing potassium efflux from neurons and blocking calcium, reducing neurotransmitter release and the firing rate of neurons. The A2A receptor is

[8] De Biasi, M. Dani, J. A. Reward, addiction, withdrawal to nicotine. Annu. Rev. Neurosci. 34, 105–130 (2011).

found in the brain's striatum and the immune cells, spleen, leukocytes, heart, and lungs. A2A receptors control the Protein Kinase A(PKA) enzyme that affects cardiac performance and peripheral cells necessary for oxygen transfer.



A2B receptors are widely expressed throughout the body but with low abundance; these receptors expressed on the neurons are the least sensitive. A3 receptors, although not affected by caffeine, serve several purposes and have been shown to be upregulated in the blood of humans with rheumatoid arthritis, Chron's disease, and colon cancer. The A3 receptors have been shown to have anti-inflammatory and anti-cancer effects.[9]These wide varieties of functions pose a challenge for Adenosine as potential drug targets.

1.4 Modulation of Pain by Sleep or Sleep by Pain

Many drugs of concern have unintentional adverse side effects on sleep quality. Therefore, they lead to more pain, suggesting a clear and bidirectional relationship between sleep quality and nociception, with most chronic pain disorders having sleeping complaints and over half of people with insomnia complaining about pain[10]. Disruption of sleep continuity results in pain as well. Many neurochemical mechanisms relate to and cause the underlying bodirectional sleep and pain relationship, such as adenosine, Nitric oxide, immune system, Hypothalamic-Pituitary-Adrenal (HPA) axis, Orexin, Norepinephrine, Melatonin, and Endocannabinoids[11]. Many of these mechanisms are altered by caffeine and nicotine uptake, such as dopamine/norepinephrine, adenosine, and

[9]Chen, J.-F., Eltzschig, H. K. Fredholm, B. B. Adenosine receptors as drug targets–what are the challenges? Nat. Rev. Drug Discov. 12, 265–286 (2013).

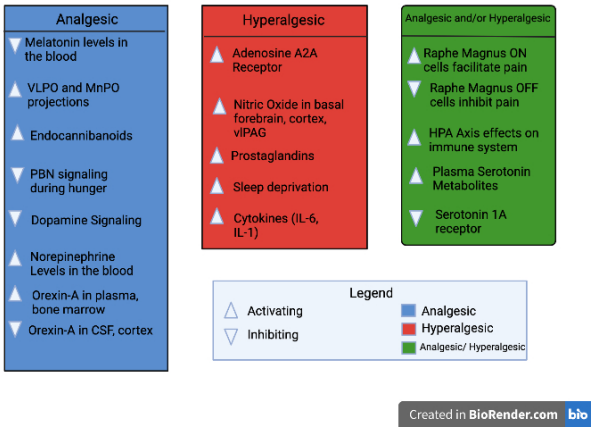
[10]Finan, P. H., Goodin, B. R. Smith, M. T. The association of sleep and pain: an update and a path forward. J. Pain 14, 1539–1552 (2013).

[11]Haack, M., Simpson, N., Sethna, N., Kaur, S. Mullington, J. Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. Neuropsychopharmacology 45, 205–216 (2020).

the immune system, which can cause changes to these mechanisms and therefore show the direct pathway on how these drugs can affect sleep or pain.

In addition to the neurochemical mechanisms, there are also specific brain regions that modulate both sleep and pain. The Raphne Magnus (RM) is involved in pain mediation and is a significant gateway to information about pain in the body and the endogenous pathways involved in pain. The RM contains serotonergic and nonserotonergic neurons that act as ON/OFF cells previously described. In addition to relating to sleep and wake states, ON cells facilitate pain, and OFF cells inhibit pain through endogenous opioids. In addition, one should note that external stimuli are less during sleep, decreasing the pain that one feels when asleep and being less sensitive to external stimuli when they are asleep.[12]

Sleep deprivation is also known to mess with descending pain inhibition modulation. In Fibromyalgia, a disorder characterized by chronic pain and poor sleep quality, there is reduced NREM sleep and A-wave intrusion during NREM Sleep, disrupting sleep cycles[13]. In addition, sleep deprivation can cause



allodynia, causing pain due to a stimulus that would not usually cause pain. In a study using c-Fos expression (a standard method used to track neuronal activity after depolarization of nerve cells) to measure neuronal activity, it was found that neurons projecting from the VLPO and median preoptic nucleus (MnPO) to the ventrolateral periaqueductal grey (vlPAG), a region that controls pain modulation, are activated during NREM sleep and provide inhibitory input to the vlPAG, reducing pain sensitivity.[14]

[12]Foo, H., and Peggy Mason. "Brainstem Modulation of Pain during Sleep and Waking." Sleep Medicine Reviews, vol. 7, no. 2, Apr. 2003, pp. 145–54.

[13]Choy, E. H. S. The role of sleep in pain and fibromyalgia. Nat. Rev. Rheumatol. 11, 513–520 (2015).

[14]Hsieh, K.-C. et al. c-Fos expression in neurons projecting from the preoptic and lateral hypothalamic areas to the ventrolateral periaqueductal gray in relation to sleep states. Neuroscience 188, 55–67 (2011).

The hypothalamus's main function is to maintain the body's homeostasis through various regulations. The hypothalamus controls hunger, thirst, body temperature, and sleep. Often, there are competing need states, such as thirst and sleep or hunger and sleep. Through the agouti-related peptide (AGRP) proteins that use parabrachial nucleus (PBN) neuropeptide Y (NPY) signaling, it was found that there was a suppression of inflammatory pain when there was a competing state of hunger.[15]. This study showed that pain could be suppressed by a competing need state, such as hunger, but the competing need state of sleep can also suppress it.

2 Mechanisms of Action of Other Drugs

Opioids are a key set of drugs that affects nociception and sleep modulation. Opioids modify gene expression, reducing neurotransmitters' excitability and nociception[16].There are four G-protein coupled endogenous opioid receptors: mu, delta, kappa, and nociceptin. Opioids also promote potassium conductance within the neuron, which means the neuron is less likely to fire an action potential. The effects of opioids on the body expand from sleep/pain but also cause sedation, anxiety reduction, and euphoria.

Opioids also bind to receptors in the Periaqueductal gray, inhibiting the pain signaling pathway in the brain via the medulla. Opioids also reduce emotional aspects of the brain by acting in the anterior cingulate cortex and increasing dopamine in the nucleus accumbens, similar to Nicotine. Repeated opioid use over time leads to tolerance as it leads to changes like a reduction in the number of functional receptors.

Another essential drug to understand is Cocaine, a common stimulant drug. Cocaine acts by blocking transporter proteins in the brain and inhibiting the reuptake of monoamine neurons such as dopamine, serotonin, and norepinephrine. Like nicotine, cocaine affects Mesocortical and mesolimbic dopamine pathways and increases projections from the ventral tegmental area(VTA) dopamine-rich area in the brain, to various locations in the limbic system and frontal cortex, like the nucleus accumbens. Cocaine causes less control over one's body, circadian disruption, and heightened stress. Cocaine disrupts the sleep architecture of NREM and REM sleep. There is a reciprocal relationship between cocaine use and sleep quality, creating a positive feedback loop for increased stress and cocaine use. Hypocretin antagonism in patients with cocaine use disorder has improved sleep, which could be a possible neurochemical link to the effect of Cocaine on the body[17].

Cocaine is also characterized by its rapid onset effects on the body from around 3-5 seconds after use. There are many reasons for this. Cocaine has two

[15]Alhadeff, Amber L., et al. "A Neural Circuit for the Suppression of Pain by a Competing Need State." Cell, vol. 173, no. 1, Mar. 2018, pp. 140–52.e15.

[16]Corder, G., Castro, D. C., Bruchas, M. R. Scherrer, G. Endogenous and Exogenous Opioids in Pain. Annu. Rev. Neurosci. 41, 453–473 (2018)

[17]Suchting, Robert, et al. "Preliminary Examination of the Orexin System on Relapse-Related Factors in Cocaine Use Disorder." Brain Research, vol. 1731, Mar. 2020, p. 146359.

different effects on the brain, the ultra-fast effects of increasing dopamine firing and the fast effects of inhibiting dopamine reuptake. These effects increase wakefulness and heighten the activity of the sympathetic nervous system, making it harder to rest/relax. These effects have lasting effects on the total time and time to fall asleep. Cocaine also blocks potassium channels of the sensory neurons in the cardiovascular system, causing increased neuronal activity there.[18]. Glutamate input to the ventral tegmental area causes dopamine release in the mesocorticolimbic pathways. Finally, the neurons are activated much more quickly in inexperienced cocaine users compared to experienced cocaine use. All of these factors cause cocaine's addictive effects and impact pain and sleep disruption.

3 Nicotine

3.1 Pain

Nicotine has been shown to reduce pain sensitivity in rats that were sleep deprived of REM and NREM sleep. However, it was found that sleep deprivation's effect on nociception is more potent than nicotine's antinociceptive effects. Specifically, the vlPAG descending pathways are those that partially sleep deprivation effect and alter.[19] The specific area nicotine affects that has to do with its antinociceptive effects is the nucleus accumbens, the part of the brain that is in the dopaminergic mesocorticolimbic pathways.

As stated before, nicotine affects the body through the nicotinic acetylcholine receptors (nAChRs), which create its high dependence and addiction rate. Nicotine has a short desensitization period to release secondary receptors such as dopamine or serotonin. This means that once nicotine is used, the period after which the neurons will not react to nicotine use is minimal. This leads to nicotine use being very frequent and impactful.[20] Nicotine also negatively impacts the spinal cord, as nicotine contracts blood vessels, making it harder for oxygen and nutrients to travel throughout the body and leading to malnourishment of the spinal discs. Nicotine leads to abnormal amygdala activity and the inability to detect harm and alters its effects on the emotional aspects of pain.

3.2 Sleep

Nicotine, although mainly impacting pain, has negative implications on sleep quality during use, withdrawal, and replacement therapy. These effects all have

[18]Wise, R. A. Kiyatkin, E. A. Differentiating the rapid actions of cocaine. Nat. Rev. Neurosci. 12, 479–484 (2011)

[19]Hirotsu, C., Pedroni, M. N., Berro, L. F., Tufik, S. Andersen, M. L. Nicotine and sleep deprivation: impact on pain sensitivity and immune modulation in rats. Sci. Rep. 8, 13837 (2018).

[20]Rosecrans, J. A. Karan, L. D. Neurobehavioral mechanisms of nicotine action: role in the initiation and maintenance of tobacco dependence. J. Subst. Abuse Treat. 10, 161–170 (1993).

to do with reducing REM and NREM sleep quality and duration, leading to daytime sleepiness. Nicotine has also increased sleep-related respiratory diseases such as sleep apnea. In addition, the effects of nicotine differ by sex; for example, nicotine patches used for replacement therapy negatively affect women's sleep quality and total wake time, while they do not significantly affect men's sleep quality. All of this shows that nicotine can cause sleep deficit from the initial time of use to the periods of withdrawal and replacement therapy.[21]

Nicotine has a variety of other side effects. A sample of students who took nicotine experienced a higher caffeine intake, more frequent problems staying awake, more daytime sleepiness, minor accidents, and depressive symptoms. Interestingly, one study found that the most susceptible group to worse sleep quality from nicotine use were Asian females. Interestingly, one study found that the most susceptible group to worse sleep quality from nicotine use were Asian females.[22]

Neurochemical mechanisms underlying the relationship between nicotine and sleep are the prefrontal cortex cholinergic neurons[23] Nicotine acts as an agonist on these receptors, increasing their activity. Another drug used in the study of the effects of nicotine on the brain is Carbachol, which has similar effects. In a study done on male rats, nicotine and carbachol decreased the latency to sleep onset. This means it took rats longer to fall asleep after the lights went out. One can see how nicotine also has negative implications on sleep through this.

3.3 Both

So, how does nicotine play into the sleep and pain relationship, and how does it alter it? Mecamylamine is a drug used to test the effects of nicotine because it is a nAChR receptor. A study that measured dorsal hippocampus nicotinic receptors induced total sleep deprivation (TSD) and REM sleep deprivation (RSD) in rats to see its effects and how nicotine may help alter them. [24].

It was found that both TSD and RSD affected memory acquisition, and both drugs reversed the effects of REM sleep on memory acquisition. Both altered pain perception and led to increased perceived pain. However, both drugs, nicotine, and Mecamylamine, reversed all behavioral changes induced by total sleep deprivation. From this, we can see that although nicotine has negative implications on sleep quality, it can help reduce certain effects of sleep deprivation, not including increased pain. Nicotine's effects on reducing nociception were not as

[21] Jaehne, A., Loessl, B., Bárkai, Z., Riemann, D. Hornyak, M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. Sleep Med. Rev. 13, 363–377 (2009)

[22] Phillips, B. A. Danner, F. J. Cigarette smoking and sleep disturbance. Arch. Intern. Med. 155, 734–737 (1995).

[23] Parkar, A. et al. Carbachol and Nicotine in Prefrontal Cortex Have Differential Effects on Sleep-Wake States. Front. Neurosci. 14, 567849 (2020).

[24] Javad-Moosavi, B.-Z., Nasehi, M., Vaseghi, S., Jamaldini, S. H. Zarrindast, M.-R. Activation and Inactivation of Nicotinic Receptnors in the Dorsal Hippocampal Region Restored Negative Effects of Total (TSD) and REM Sleep Deprivation (RSD) on Memory Acquisition, Locomotor Activity and Pain Perception. Neuroscience 433, 200–211 (2020).

strong as sleep deprivation's hyperalgesia (increased pain).

4 Caffeine

4.1 Pain

Caffeine has a paradoxical effect on pain; it can inhibit and elicit pain. Caffeine has been shown to supplement Non-steroidal anti-inflammatory drugs(NSAIDs) when taken in medial amounts and augment their effects in pain inhibition.[25] Examples of NSAIDs include Aspirin and Ibuprofen. However, caffeine in high amounts causes addiction and can lead to more headaches during the withdrawal of caffeine. Another thing to note is that caffeine can inhibit the effects of Transcutaneous Electric Nerve Stimulation (TENS) and reduce its effects as a pain therapy.

But how does caffeine block pain? Caffeine blocks pain by acting as an antagonist of the A1 and A2A adenosine receptors on skeletal muscle nerve endings. The antagonistic effects of caffeine on adenosine make caffeine's effects have not only implications on sleep but also other implications on pain modulation. However, in the study that found this, pain is defined as the intensity of "hurt," which does not necessarily translate to pain.[26]

4.2 Sleep

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It is well known that caffeine has negative implications on sleep. But what are the different effects that caffeine has on sleep? In addition to reducing total sleep time, it can also delay the 24-hour circadian clock: making it hard to fall asleep. It was found that consuming around 200 mg of caffeine (2 shots of espresso) created a 40 min delay in sleep time on average.[27] Also, consuming caffeine six hours before sleep reduces total sleep time by one hour. Caffeine can also help anesthesia emergence. There are no current drugs to reverse anesthesia and its effects of it. However, in a study on eight healthy males, caffeine aided in the emergence of isofluorane anesthesia.[28] This was measured by the Sternberg Memory Test and Divided Attention Task and other related cognitive tasks. Caffeine has various adverse effects on sleep but can also aid in anesthesia emergence. Anesthesia and sleep are not the same; while anesthesia also has analgesia (cannot feel pain) and muscle paralysis, sleep does not have either of these characteristics.

[25] Sawynok, J. Caffeine and pain. Pain 152, 726–729 (2011).

[26] Gliottoni, R. C., Meyers, J. R., Arngrimsson, S. A., Broglio, S. P. Motl, R. W. Effect of caffeine on quadriceps muscle pain during acute cycling exercise in low versus high caffeine consumers. Int. J. Sport Nutr. Exerc. Metab. 19, 150–161 (2009).

[27] Burke, T. M. et al. Effects of caffeine on the human circadian clock in vivo and in vitro. Sci. Transl. Med. 7, 305ra146 (2015).

[28] Fong, R. et al. Caffeine Accelerates Emergence from Isoflurane Anesthesia in Humans: A Randomized, Double-blind, Crossover Study. Anesthesiology 129, 912–920 (2018).

4.3 Both

As explained above, adenosine receptors link the caffeine and pain relationship. However, adenosine has many different purposes in addition to just those two. Adenosine controls many neurodegenerative diseases such as Alzheimer's and Parkinson's.[29] Over-caffeine consumption can have preceding effects on different neurodegenerative diseases, pain, and anxiety. Adenosine is known to control the 'flow' of the brain, controlling many things and ensuring all interactions are balanced and controlled. Caffeine desynchronizes this flow and has potential long-term effects. Finally, caffeine alters calcium influx into nerve cells, altering blood flow in the brain and killing nerve cells. Caffeine also interferes with the inhibitory effects of GABA-A compounds. From all of this, one can see that caffeine has many negative effects on the brain, both short-term and long-term.

5 Conclusion

What one can take away is that these drugs are very commonly used and on the rise, yet many people do not know how these drugs affect their bodies in many ways. Although these drugs can have some positive effects, like reduced nociception and increased alertness, they tend to have a multitude of other poor effects, such as reduced wave sleep and REM sleep, depressive symptoms, increased anxiety, and preceding effects on common neurodegenerative disease. These negative effects outweigh the positive effects. In a world with increasing stress and pressure to succeed, sleep tends to be more sparse, and drugs of abuse tend to be a coping mechanism for those with increased pressure to succeed. Many do not know about this underlying relationship between drugs and sleep, and it may become a more significant problem moving forward, which needs to be studied more. Perhaps more and more sleep studies need to be funded where there is a large proportion of drug users.

6 Acknowledgements

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