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Review

# Substances of Abuse and Collateral Brain Hypoxia

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## Abstract

This paper explores the notion that substances of abuse may induce a collateral brain hypoxia as part of their effects, which may boost euphoria and dopamine availability within the brain. Further, that frequent hypoxias may deplete the endogenous neurotransmitters of the brain, which may lead to cravings and contribute to addiction. Tolerance is contemplated as a misnomer for the cumulative dopaminergic pathway damage that is thought to occur after repeated substance induced brain hypoxias. The role of substance abstinence is discussed in the context of dopaminergic pathway damage. Novel pathway generation is contemplated in the treatment of addiction.

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## Orientation

Psychedelics, opiates, ethanol (ethyl alcohol) and other substances of abuse are known for their euphoria and "mind bending" characteristics such as dissociation, auditory and visual hallucinations.

Their effects also include neurotransmitter anomalies, cerebrospinal fluid anomalies and intracranial pressure changes. Blood brain barrier disruptions may occur and glucose transport may be affected (1,2,3,4). Many substances of abuse can enter the brain nearly unopposed via the blood brain barrier (BBB) and can be addictive, especially after frequent abuse (5). Research on their mechanisms of action continues while many questions remain unanswered.

## Substances of Abuse and Collateral Brain Hypoxia

This paper explores the notion that substances of abuse may trigger a collateral brain hypoxia that may boost euphoria and contribute to addiction when endogenous neurotransmitters in the brain deplete. Such collateral brain hypoxias may occur through various mechanisms including carbon monoxide exposure, diffusion hypoxia, cerebral vasoconstriction, respiratory depression and deoxygenation through substance metabolism. Human and animal studies have shown that brain hypoxia can increase striatal dopamine by fivefold or more at onset, also other neurotransmitters such as glutamate and the neuroprotective neurotransmitter GABA (6,7,8,9).

## Hypoxia and Euphoria

Several situations show a possible link between hypoxia and euphoria. Altitude euphoria is a well-known phenomenon in mountaineers above 3000 meters where oxygen decreases by more than 25 percent compared to sea level. In high lying areas such as Utah, USA, a lack of oxygen has been implicated as a cause for psychological idiosyncrasies in its population (10,11,12). Euphoria has been attributed to a potentially fatal behaviour called the strangulation game, which creates a brain hypoxia by strangulation (13). Respiratory diseases with hypoxia have been associated with euphoria. In 2020 some dangerously hypoxemic COVID-19 patients remained unperturbed by their serious medical condition, mildly euphoric with no signs of dyspnoea or distress (14).

Clarke et al contemplated brain hypoxia as a cause of euphoria in a group of teenagers accidentally exposed to carbon monoxide poisoning from a faulty kitchen boiler (15).

Carbon monoxide is a gaseous combustion product that blocks the oxygen binding capacity in the blood which can result in hypoxemia and eventually brain hypoxia. Carbon monoxide from cigarette smoking can block up to 10 percent of oxygen binding capacity in the blood (16). Interestingly, there is an association between cigarette smoking and an escalating substance use over time (17).

Nitrous oxide (laughing gas) is sometimes used as a rapidly absorbed gaseous party drug which can displace respiratory oxygen directly or indirectly by diffusing back into the lungs on first pass circulation. This crowds out ventilatory air exchange and impairs the oxygenation of the blood. A resultant hypoxemia may trigger brain hypoxia. Reactionary neurotransmitter surges may occur, including dopamine, which may enhance euphoria (18).

## Substance Use and Cerebral Vasoconstriction

High dose ethanol abuse is associated with cerebral vasoconstriction and likely brain hypoxia. It can manifest as full intoxication at its maximum, with neurotransmitter surges and euphoria (19, 20). Previous studies have shown that hypoxia at altitude can bolster the effect of ethanol before full intoxication is achieved (21, 22).

Studies show that cerebral vasoconstriction and inflammation can occur upon cocaine consumption, which reduces cerebral blood flow (23). A reversible cerebral vasoconstriction syndrome is often encountered through excessive use of cocaine, associated with so-called thunder clap headaches (24, 25). The phenomenon is also seen after cannabis (marijuana) and with amphetamines or opiates. Research shows that psilocybin decreases cerebral blood flow in parts of the brain, while headaches can be encountered as a complication of its use (26, 27).

## Endogenous Neurotransmitter Shortages

Most substances of abuse contain less molecular oxygen than their metabolites. Oxygen has thus to be sourced inside the brain when substances of abuse are broken down to their metabolites by oxidation or via glucuronidation (28). Such oxygen has to be obtained directly from the blood or indirectly from other sources in the brain, likely oxygen rich Krebs cycle constituents or forerunners destined for neurotransmitter synthesis inside the brain. The overuse of oxygen or the poaching of oxygen rich molecules or neurotransmitter forerunners may lead to synthesis deficiencies in the brain. Neurobiological damage due to hypoxia may lead to further synthesis deficiencies and consequently neurotransmitter shortages inside the brain.

Researchers at the University of Texas found that chronic use of cannabis increases brain oxygen extraction fractions over time (28). Cannabis metabolites are glucuronidated, which consumes glucuronic acid, which can be sourced from glucose and molecular oxygen inside the brain (29). Methamphetamine breaks down to amphetamine, then to hydroxyamphetamine and other metabolites (30). Such metabolites contain more oxygen than amphetamine. Animal studies have shown that LSD (lysergic acid diethylamide) impairs oxygenation within the brain (31). LSD requires oxygen to convert to its metabolites, particularly to its most common metabolite, 2-oxo-3-hydroxy-LSD.

Respiratory depression is a well-known side effect of substances of abuse, particularly opiates. Hypoxemia and hypercapnia during hypoventilation can trigger chemosensory and compensatory feedback mechanisms in the brain, thought to be overwhelmed and ineffective during opiate abuse (32).

This paper proposes that substance induced brain hypoxias deplete the endogenous neurotransmitters in the brain through overuse, synthesis bottlenecks and ATP anomalies that influence synaptic transporter systems. Particularly dopamine can deplete from pools of its abundance such as the striatum and reward circuits of the brain.

## Hypoxia and Cerebral Blood Flow

Hypoxia boosts cerebral blood flow at first and later slows it down. The boost occurs particularly in the striatum and dopaminergic regions of the brain, with concurrent neurotransmitter surges including dopamine, glutamate and GABA. A slowing down then follows. Intracerebral steal may occur, which can divert cerebral blood flow to parts of the brain that have a lesser vascular resistance (33). A further mechanism is diaschisis, which is the downregulation of a part of the brain that is neurologically connected to a site of brain dysfunction during hypoxia or ischemia (34). It can occur in most parts of the brain, including the cerebrum, cerebellum and basal ganglia, which can be ipsi- or contralateral to the site of brain dysfunction. It may be linked to an area of neurodormancy which is thought to be a GABA based neurobiological downregulation of a part of the brain that has been exposed to long term brain hypoxia and ischaemia (35,36).

## Effects on the Blood Brain Barrier

Most substances of abuse can affect the BBB with inflammatory changes and increased permeability (37). This enables undue molecular components to pass from the blood into the brain, but also from the brain into the blood. Losses from the brain such as neurotransmitters or their building blocks may occur, which could worsen neurotransmitter shortages inside the brain.

## Dopaminergic Pathway Damage

Dopaminergic pathways are an important component in the reward systems of the brain. They are found in the striatum, ventral tegmental area, nucleus accumbens, prefrontal cortex and other parts of the brain.

Dopaminergic pathways are particularly vulnerable to brain hypoxia. They have an increased dopaminergic and glutamatergic response to hypoxia, but a limited GABA response (40, 41, 42). This limits GABA based neuroprotection during hypoxic events and leaves such pathways vulnerable to collateral neurobiological damage, possibly micro infarctions. The nucleus accumbens can shrink over time after excessive substance use. Such a shrinkage is seen in Parkinson's disease also, for which there is a 300 percent increased risk after long term substance abuse (43, 44).

## Addiction and Tolerance

Addiction is thought to occur when reward pathways of the brain are hijacked by substance abuse, which triggers an excessive dopamine release initially. This creates an intense euphoria that overrides the natural regulatory mechanisms of the brain. Tolerance develops over time as available dopamine and its receptors decrease in the brain (45).

This paper proposes that "tolerance" is a misnomer for the neurobiological damage that occurs in the dopaminergic pathways of the brain after repetitive hypoxias that are associated with substances of abuse. Substance users may yearn for feelings of euphoria when they stop using their substance of abuse. Such feelings may form a part of a downward spiral of progressive neurobiological damage, particularly in the dopaminergic pathways of the brain. The more the damage the less the available dopamine and its receptors, and the higher the dose of substance that is required to achieve euphoria or even a level of emotional normalcy after substantial pathway damage. A desire to remedy such shortages may present clinically as cravings and progress to addiction.

## Neuroglycopenia

It is known that hypoxia increases insulin resistance within the brain which may limit its access to glucose (46). This may inhibit Krebs cycle function, consequently neurotransmitter synthesis and energy production inside the brain. Neuroglycopenia refers to a shortage of glucose inside the brain that can occur after years of substance abuse and addiction (47).

## Cerebrospinal Fluid Effects

It is proposed that substances of abuse can influence cerebrospinal fluid composition inside the brain. Cerebrospinal fluid (CSF) needs to maintain a specific osmolarity which is preserved by active molecular transport which depends on ATP, which depends on oxygen availability (43). It is proposed that lowered ATP production during substance induced hypoxias may result in lower active transport capabilities within the brain, which may influence CSF composition and its osmolarity, consequently intracranial pressure.

## Novel Pathways

Once addiction has commenced, the circuit damage will persist, even after substance abuse has stopped. Neurodormancy can be reversed to an extent, but not the cumulative neurobiological damage that is caused by brain hypoxia. The longer the abuse, the more the damage and the less the chance of functional revival.

Medications can be used as neurotransmitter substitutes or for psychological symptom relief, but a true emotional homeostasis will only be achieved by newly generated circuits that negate the effect of the defective older ones. Substance users may need to change their behaviour and motivational concepts. They may have to create a “new persona” for themselves. Gross lifestyle changes and cognitive behavioural therapy may be helpful to generate such novel circuits (49). Multi-step recovery plans and motivational interviewing techniques may help (50, 51). Newly established circuits will be vulnerable to hypoxic damage too. A permanent cessation of substance use may be necessary for addiction therapy to succeed.

## Conclusion

The above considerations show that substance induced brain hypoxias may play a role in the mechanisms of substances of abuse. Collateral brain hypoxias may boost euphoria at first, but later lead to dopaminergic pathway damage, which may lead to decreased dopaminergic effects and pathway function. Depletion of the endogenous neurotransmitters in the brain may lead to cravings and contribute to addiction.

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