Review Article

A Review of Neuropharmacological Mechanisms of Amphetamine-Induced Euphoria: From Dopamine Signaling to Addiction Pathways

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ABSTRACT

Amphetamines are a class of compounds with complex histories in both pharmacology and neuroscience. Notably, while amphetamines have been shown to have therapeutic applications, including treating conditions such as Attention Deficit Hyperactivity Disorder (ADHD), they can also be misused due to their ability to produce strong euphoric feelings through their action on the dopamine system. The strong euphoria experienced after consuming amphetamines occurs because they increase the release of dopamine in certain brain regions that are associated with pleasure/reward, most notably, the mesolimbic area; and therefore, they create a great deal of pleasure and reinforce users' behaviours regarding continued use of amphetamines. Continued use of amphetamines modifies the brain's reward circuitry, thus contributing to the development of tolerance, physical dependence, and ultimately addiction. In addition to reviewing the history of amphetamines and their neuroanatomical mechanisms, this article will describe how there is substantial variability between individuals in their response to the euphoric effects of amphetamines, as well as potential implications for clinicians and other professionals working with clients experiencing the negative effects of amphetamines. Lastly, molecular evidence, neuroimaging evidence, behavioural evidence, and clinical observations will all be integrated to facilitate a more complete understanding of how amphetamines affect the way that the brain operates. Taken together, the body of evidence will demonstrate how the euphoric effects of amphetamines can reinforce their use and encourage the progression from first exposure to substance abuse and eventual dependence/addiction.

Keywords: Amphetamine, euphoria, dopamine, reward pathway, psychostimulants, addiction neurobiology.

INTRODUCTION

Amphetamine is a powerful stimulant drug (psychostimulant) that has had an impact on the fields of clinical medicine, neuroscience and public health for almost a century. Originally, amphetamine was used to treat sleep disorders (narcolepsy), mood disorders (depression) and attention disorders (attention deficit disorder) as a medical drug; however, it later became a drug misused by people who wanted to be awake, energized and euphoric [1]. Clinical studies done early on suggested that two of the key subjective experiences associated with taking amphetamine were having your mood improved and feeling good – this helped researchers identify the reinforcing properties of amphetamine [2]. Current neuropharmacological studies have shown that amphetamines are normally used by increasing the amount of monoamines – particularly, dopamine – in the synapses via transporter-mediated release and reuptake inhibition, leading to activation of mesolimbic reward systems [3].

Amphetamine's ability to increase dopamine output in the ventral striatum is confirmed by neuroimaging studies and correlates positively with reports of euphoric feelings, indicating dopamine's crucial contribution to the reward and motivational systems of the brain[4]. Responses to amphetamines can differ widely from one individual to another based on genetics, behavioral characteristics, and the environment [5]. Although amphetamines have been used clinically, repeated use can result in neuroadaptative changes, a physical dependence on the drug, as well as toxicity, making it essential to have a thorough understanding of how these processes work and how they might play out in a clinical setting [6]. The focus of this review is to examine the neural mechanisms behind amphetamine-euphoria and to determine their importance for addiction and potential treatment strategies.

Historical and Pharmacological Overview

Discovered during the 20th century, amphetamines were first manufactured to treat narcolepsy, depression, fatigue, and to suppress appetite due to its stimulant properties on the CNS [7]. As the decades passed, the use of amphetamine therapeutically expanded rapidly in the 1950s. However, the strong euphoric and mood-boosting properties of amphetamine led to widespread non-medical amphetamine use and eventually increased concerns about the potential for misuse/abuse and dependence [8]. The focus of research transitioned from solely examining amphetamines from a therapeutic standpoint, to understand their neurobiological mechanisms that reinforce their addictive properties. Pharmacologically, amphetamines primarily interact with monoamine transporters (dopamine, norepinephrine, and to a lesser extent serotonin). By reversing transporter functions and disrupting vesicular storage, amphetamines increase the concentration of catecholamines outside the cells and

facilitate increased neurotransmission in brain areas associated with reward [9]. These increases in dopamine (within the mesolimbic pathway) are believed to be responsible for the stimulant and euphoric effects of amphetamines as well as rewards obtained from any other substance, mystery, or behaviour [10].

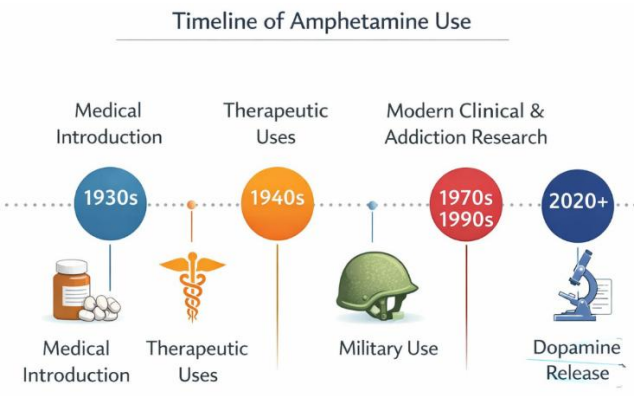

Figure 1: Timeline of Amphetamine Use

As per the Drugs of Abuse: Pharmacology and Molecular Mechanisms and Monoamine Transporters mechanistic models, the monoamines transporters dynamics form the primary mechanism that drives the psychostimulant effects of amphetamines. The amphetamines enter the presynaptic terminal through both the dopamine transporters (DAT) and norepinephrine transporters (NET) and disrupt the vesicular monoamine transporter-2 (VMAT2), which causes dopamine to load into the cytoplasm instead of being stored in the vesicles. In addition, the increased concentration of dopamine occurs through an alteration in the direction of transport in both DAT and NET, which leads to the reverse transport of dopamine into the synaptic cleft. These elevated concentrations of dopamine in the synaptic cleft enhance the stimulation of postsynaptic dopamine receptors, and thus increase feelings of arousal, reward, and euphoria. The following figure synthesizes the four sequential processes through which amphetamines produce behavioral and clinical effects by illustrating how molecular-level interactions produce these effects.

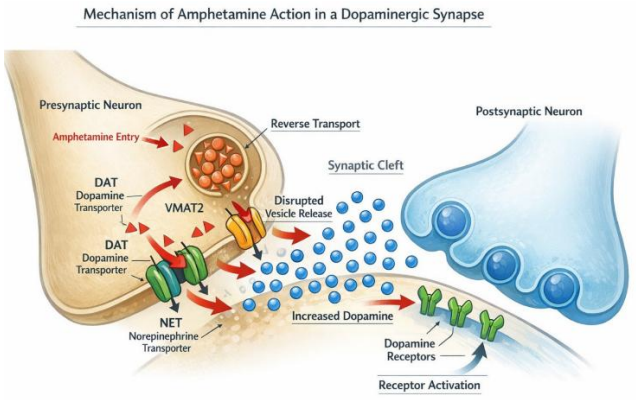

Figure 2: Mechanism of Amphetamine Action

This knowledge is necessary to interpret the therapeutic effects of amphetamines in selected therapeutic environments as well as the neurobiological mechanisms of misuse, tolerance, and dependence due to repeated exposure to amphetamines [11].

Neurobiology of Amphetamine-Induced Euphoria

1. Dopamine and the Mesolimbic Reward System

Much of the evidence supporting the association between amphetamines and euphoria is based on the release of dopamine that occurs in the ventral striatum, which is the primary structure in the brain associated with reward processing. Studies utilizing positron emission tomography have demonstrated that increases in dopamine due to amphetamine correlated with participants' subjective ratings for euphoria, confirming the important role of dopamine in reward derived from stimulants [12]. Similarly, results from studies involving healthy individuals have confirmed that dopaminergic activation contributes to the reinforcing and pleasurable effects of amphetamine [13]. Dopamine released physically serves an important role in predicting rewards, indicating motivation, and facilitating reinforcement learnin [15], while the transmission of dopamine in the dorsal striatum plays an important role in motivation and action selection [16]. Collectively, these mechanisms serve to explain how amphetamine converts neutral environmental stimuli into highly rewarding and behaviorally relevant stimuli.

Figure- Mesolimbic Reward Pathway and Euphoria illustrates how amphetamines facilitate the flooding of dopamine into the nucleus accumbens and prefrontal cortex through a mechanism of increasing the amount of dopamine released from neurons, which originate in the ventral tegmental area (VTA). As this figure suggests that the increased activity of the mesolimbic reward system through enhanced dopaminergic signaling leads to increased drug-seeking behavior and ultimately creates a sense of euphoria, the relationship between the regional brain circuitry and the dynamic nature of dopamine release established between them may be a significant factor in how simple molecular pharmacological activity can produce very complex behavioral effects following reinforcement and ultimately addiction[17].

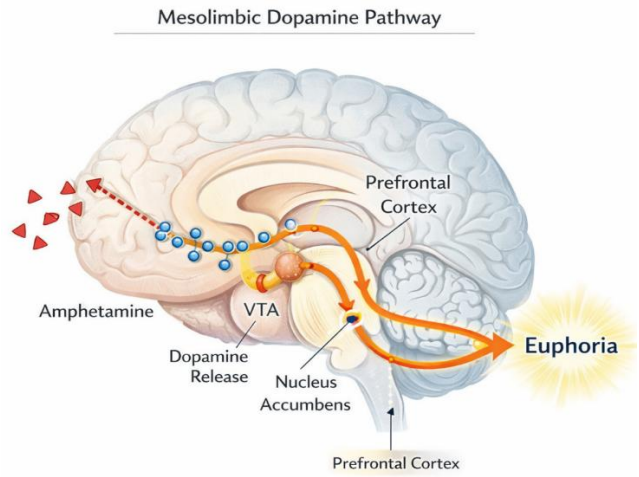

Figure 3: Mesolimbic Reward Pathway and Euphoria

2. Dopamine Signaling Dynamics

Studies conducted recently have demonstrated that dopamine signaling is not strictly a neuronal process; glial cells and environmental factors also contribute greatly to modulating the transmission of rewards through neurotransmitter chemistry. Connections between astrocytes and neurons within mesolimbic pathways play a role in the regulation of synaptic activation and therefore affect dopamine-mediated transmission/communication, or reward signaling, and point to the complexity of these networks [18]. The role of dopamine in communication extends far beyond its function as a neurotransmitter; it has taken on an additional role in the regulation of inflammation and plasticity, which has implications for brain homeostasis and disease adaptability or recovery from brain injury or illness [19]. These new findings illustrate that dopamine cannot only be defined exclusively as a biological marker of reward; there are also important and complex mechanisms of regulation of behavior after exposure to psychostimulants.

As shown in Figure-Transporter-Level Mechanism, the molecular level interactions of the transporters (dopamine) are crucial to the dynamics of dopamine. In particular, that amphetamine interacts with monoamine transporters (e.g., DAT, and NET) to stimulate retrograde transport of dopamine and increase extracellular (or synaptic) concentrations of dopamine. These mechanisms of action (i.e., transporter-mediated) create not only an enhanced, but also a molecular environment that may modify glial cell activity and synaptic plasticity (changes in the connection between neuronal cells) through molecular transporter function at the transporter, and network level, ultimately altering the reward process, reinforcing certain behaviors and leading to chronic neuroadaptations associated with repeated amphetamine administration[19].

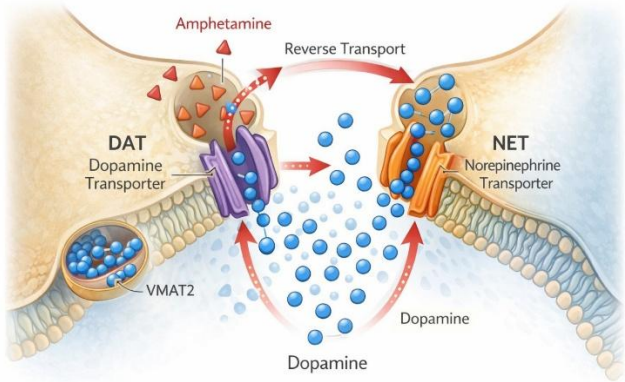

Figure 4: Transporter-Level Mechanism

3. Non-Canonical and Modulatory Mechanisms

Non-Canonical and Modulatory Mechanisms

There is a growing body of research that indicates that in addition to the classical model of dopaminergic signaling (i.e., dopamine release and interaction with its receptors), there are also numerous other ways in which dopamine (or dopamine receptor) functions can be altered through non-canonical and adjuvant pathways. This new information leads us to conclude that there is more to dopamine activity than meets the eye; there are additional ways to modulate dopamine's effects through other types of cell-receptor interactions than only those between dopamine and its receptor(s). For example, D1-mGlu5 receptor heteromers allow for altered signaling through alternative pathways (i.e., they can serve as a receptor complex) and influence plasticity at the synapse, neuronal excitability, and behaviors resulting from the use of psychostimulants like amphetamines [20]. These two types of receptor complexes, when activated, allow for communication between the dopaminergic system and the glutamatergic system which can modulate the intensity and duration of the pathways responsible for the reward and pleasure generated from psychostimulant use.

Receptor heteromerization is just one of many ways by which different types of modifications can alter the manner in which a person experiences the euphoria induced by amphetamine over time. Other possible forms of modulation include: modulation of intracellular second-messenger systems; modification of the receptor, as in sensitization; adaptation or modification through neuroplastic changes. All of these processes can help to explain differences in individuals' subjective experience, reinforcing properties, and vulnerability to compulsive drug-seeking behaviour; therefore, genetic, environmental and previous drug-exposure factors may also contribute to variability across these pathways, providing an explanatory model for individuals who develop greater sensitivity to the euphoric effects of amphetamines and greater risk for developing a use disorder compared to others. Investigating these numerous modulating systems is important to developing a better understanding of the neurobiological processes by which amphetamine works and opening new areas for the development of therapeutic approaches for reducing the misuse and/or dependency on stimulants [20].

Human Subjective Experience and Individual Differences

Human responses to amphetamine vary considerably despite similar pharmacological exposure, indicating that subjective effects are shaped by multiple biological and psychological factors. Individual variability in euphoria, stimulation, and reinforcement sensitivity plays an important role in determining vulnerability to repeated use and potential dependence. Research integrating genetics, behavioral traits, and emotional processing has provided valuable insight into why amphetamine produces strong euphoric experiences in some individuals while others experience milder or less reinforcing effects [21].

1. Genetic Influences

Genetic variability is a major contributor to differences in subjective responses to amphetamine. Studies have shown that polymorphisms in the OPRM1 gene, which encodes the mu-opioid receptor, significantly influence the intensity of amphetamine-induced euphoria [22]. These findings suggest functional interaction between dopaminergic reward

pathways and endogenous opioid systems, indicating that reward processing is mediated by interconnected neurotransmitter networks rather than dopamine alone. Genetic differences may alter receptor sensitivity, dopamine release dynamics, and reward perception, thereby influencing individual susceptibility to stimulant misuse and addiction vulnerability.

2. Sex and Behavioral Differences

Sex-based differences further contribute to variability in amphetamine responses. Evidence indicates that behavioral traits such as sweet taste preference are associated with stronger subjective effects of amphetamine in women but not in men, highlighting potential hormonal or neurobiological influences on reward sensitivity [22]. Additionally, amphetamine alters emotional reactivity, influencing responses to affective stimuli and potentially modifying social and motivational behavior [23]. These findings emphasize the importance of considering sex as a biological variable in psychostimulant research.

3. Psychological and Behavioral Correlates

Psychological characteristics, including inhibitory control and baseline reward sensitivity, also modulate amphetamine-induced experiences. Individuals with reduced inhibitory control or heightened neural responsiveness to reward cues may be more vulnerable to reinforcing stimulant effects [24]. Furthermore, personal mood history and prior experiences with mood elevation can alter subjective responses, potentially increasing the likelihood of repeated use and misuse (Schepers et al., 2019). Together, these genetic, behavioral, and psychological factors highlight the multifactorial nature of amphetamine-induced euphoria and help explain substantial inter-individual differences in risk for dependence.

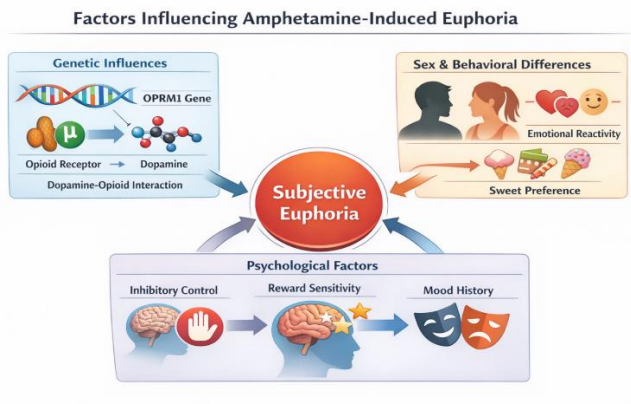

Figure 5: Factors Influencing Amphetamine-Induced Euphoria

From Euphoria to Dependence

Although euphoria initially reinforces use, repeated exposure leads to neuroadaptations associated with craving, tolerance, and compulsive use [25]. Neurochemical changes involve oxidative stress, neuroinflammation, and altered dopamine transporter function.

Historical clinical studies found that dopamine antagonism does not fully block amphetamine euphoria [26], indicating multi-neurotransmitter involvement.

Toxicological and Forensic Perspectives

Amphetamine toxicity involves oxidative stress, excitotoxicity, and neuronal injury [26]. Advances in forensic detection include enantioselective LC–MS/MS techniques distinguishing synthetic pathways and usage patterns [27].

ELISA-based assays now detect multiple designer amphetamines in biological fluids [28], highlighting evolving drug landscapes.

Clinical Management and Pharmacotherapy

1. Pharmacological Treatment Strategies

Systematic reviews indicate limited but emerging efficacy for pharmacotherapies targeting amphetamine dependence [28]. No universally effective medication currently exists, reflecting the complexity of stimulant reward mechanisms.

2. Non-Pharmacological Interventions

Acute aerobic exercise shows promise in reducing craving and improving attentional function in methamphetamine users [29]. Such approaches may modulate dopamine signaling without pharmacological risks.

Broader Dopamine Context

Modern dopamine research extends beyond reward into immune modulation and neuroinflammation, indicating broader physiological roles [30]. These findings suggest future therapeutic approaches may target network-level signaling rather than dopamine alone.

Societal and Behavioral Perspectives

Qualitative studies reveal that users sometimes self-medicate with methamphetamine for functional purposes, including opioid withdrawal management [31]. This highlights the interplay between subjective euphoria and perceived utility[32].

Future Directions

Future research should emphasize:

- personalized approaches considering genetics and sex differences[33],
- multi-system models including glial and immune signaling,
- improved pharmacotherapies targeting reward circuitry[34],
- integration of behavioral interventions with neurobiological insights[35].

CONCLUSION

Amphetamine-induced euphoria arises primarily from enhanced dopamine signaling within mesolimbic circuits but is shaped by genetic, behavioral, and neurobiological

modulators. While euphoria contributes to therapeutic interest historically, it also underlies significant abuse liability. Advances in neuroimaging, molecular neuroscience, and clinical research are revealing increasingly complex mechanisms that may guide future treatments for amphetamine use disorder.

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