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REVIEW
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Dopaminergic and Glutamatergic Mechanisms in Addiction: Assessing the Therapeutic Promise of Memantine and Galantamine for Maintenance Treatment: A Review

ABSTRACT

Addiction comes in various forms and can be related to substances like cocaine, opioids, alcohol, cannabis, amphetamine, and nicotine, as well as behaviors like gambling or sex addiction. The impact of addiction places increased economic and medical burdens on society. Currently, the management of addiction is more focused on symptomatic relief rather than targeting the reinforcing mechanisms of dependence on addictive substances and behaviors. The aim of this review is to identify the specific roles of dopamine and glutamate in addiction, which can guide us to treat the cause rather than the symptoms. The synergistic effect of glutamate and dopamine neurotransmitters plays a crucial role in the development of pathological neuroplasticity in the mesolimbic system, causing compulsive consumption of the substance. Utilizing the brain's natural synthesis of substances such as Kynurenic acid (KYNA) derivatives could potentially disrupt the synergistic effect of glutamate and dopamine. By blocking glutamate release and increasing dopamine release, individuals may experience reward or pleasure without the need for addictive substances. Under this pretext, the review article explores the possibility of memantine and galantamine as maintenance treatment for addiction of various forms.

Keywords: Addiction, behavioral addiction, neuroscience, substance abuse, treatment

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Pleasure, Reinforcement, and Addiction

Addiction involves pleasure-driven behavior,[1] raising the question: Is pleasure seeking a normal human experience? The mesolimbic dopamine pathway, known as the "hedonic pleasure pathway", and dopamine, labeled the "neurotransmitter of hedonic pleasure," play crucial roles in this context.[2] Everyday accomplishments, victories, or even an orgasm can release a sense of pleasure often referred to as a "natural high."[2] The brain's neurons naturally release neurotransmitters similar to substances such as acetylcholine (nicotine), endorphins (morphine/heroin), cannabinoids (cannabis/marijuana), and dopamine itself (cocaine and amphetamine), all leading to common pathways that drive pleasure. However, the stimulation of dopamine by addictive substances is much more intense, explosive, and creates more pleasant experiences than the natural pleasure process.[2] This requires an understanding of the distinction between "reward" and "reinforcement."

Subjective hedonic states, such as euphoria, may be linked to reward, but post-substance consumption, reinforcement correlates with increased future behavioral responses.[3] Individuals exhibit behaviors that boost the likelihood of obtaining "positive reinforcers," such as pleasure, while simultaneously raising the probability of avoiding "negative reinforcers," such as anxiety or withdrawal symptoms.[3] Classical or Pavlovian conditioning, which involves associations between unconditioned and conditioned stimuli, is instrumental in understanding positive reinforcement.[3] An example from Pavlov's dog experiments illustrates this concept: the dogs salivated (conditioned response) at the sound of a bell (conditioned stimulus) with the presence of food (unconditioned stimulus).[4] In the context of addiction, pleasure obtained from being in environments or with people linked to easy drug access (conditioned

stimuli) can lead to drug-seeking and drug-taking behaviors (conditioned response), constituting positive reinforcement in the addiction context. However, drug-seeking and drug-taking behaviors are conditioned responses to conditioned stimuli, such as experiencing cravings and withdrawals, constituting negative reinforcement in addiction.[2]

Neurobiology of Addiction

The phases involved in addiction include.[5]

1. Active phase.
2. Excessive drug intake.
3. Phase of more controlled use.
4. Phase of abstinence.
5. Episodes of relapse.

Pathologically, the addiction cycle can be divided into 4 stages as follows[6]:

1. Intoxication stage: positive reinforcement and stimulation of dopamine in the ventral striatal regions during initial drug use.
2. Habitual stage: stimulation of dopamine in dorsal striatal regions.
3. Withdrawal stage: hypoactivity of the dopamine system and hyperactivation of the stress system. This negative effect causes people to use drugs not for their positive effects, but to alleviate negative emotional states.
4. Preoccupation/anticipation stage: activation of cortical areas and release of dopamine in regions related to emotion and memory, such as the amygdala and hippocampus (Hip), leading to drug cravings.

The intricate molecular mechanisms that underlie drug addiction encompass various cerebral regions, including the prefrontal cortex (PFC), ventral tegmental area (VTA), nucleus accumbens (NAc), and the Hip.[7] Within this constellation of regions, the VTA, situated near the midbrain, plays a crucial role in the reward mechanism.[8,9] The cellular composition of the VTA is composed of 3 principal neuronal subtypes: dopamine neurons, accounting for 60%-65% of cells; GABAergic neurons, encompassing 30%-35% of cells; and glutamate neurons, comprising 2%-3% of cells.[10]

Glutamate, an excitatory neurotransmitter, participates in the addiction reward pathway through its ionotropic receptors, specifically the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-Aspartate (NMDA) receptors.[11] These receptors modulate the flow of calcium, potassium, and sodium ions in and out of cells by binding to ligand-gated channels.[11] In the VTA, glutamatergic neurons-expressing vesicular glutamate transporter 2 (VGLUT2) project to limbic and cortical regions, exciting neighboring dopaminergic neurons[12] VGLUT2 is also present in dopaminergic neurons projecting from the VTA to the NAc,[13] emphasizing the interaction between glutamate and dopamine in shaping post-synaptic AMPA receptor plasticity.[14]

The rewarding path of addiction involves 3 dopamine pathways: mesolimbic (MLDP), mesostriatal (MSDP), and mesocortical.[15] In MLDP, VTA dopamine cells project to NAc, located in the ventral striatum, stimulating the reward system and leading to an increased sense of pleasure.[15] Mesostriatal involves dopamine cells from the substantia nigra projecting to the dorsal striatum, including the caudate nucleus and putamen, contributing to drug habituation and addiction.[15] In the mesocortical pathway, dopamine cells in the VTA project to the medial prefrontal cortex, leading to the release of dopamine from the amygdala and Hip, resulting in drug craving behavior.[15] Stimulants, nicotine, alcohol, and marijuana (cannabis) trigger the release of dopamine in the dorsal and ventral striatum, where the NAc is located, highlighting the role of dopamine in drug-induced pleasure.[15]

Addiction is associated with alterations in neuroplasticity in the mesolimbic system.[16] Structural plasticity refers to the reorganization of synaptic connections in brain circuits.[17] Prolonged exposure to drugs induces enduring alterations in both excitatory and inhibitory inputs into dopamine neurons within the VTA.[18] Examination of synaptic plasticity commonly involves the study of excitatory synaptic transmission, specifically by analyzing excitatory postsynaptic currents mediated by the AMPA/NMDA ratio (EPSC).[16] Chronic drug usage results in an increase in the AMPA/NMDA ratio at excitatory synapses in VTA dopaminergic neurons.[19] Concomitantly, prolonged exposure to drugs induces an increase in dendritic spine density in the PFC and NAc, contributing to the reinforcement of the reward mechanism.[17] These enduring structural modifications significantly contribute to the persistence of drug addiction.[17]

Beyond the involvement of dopamine, glutamatergic neurons play a notable role in the dynamics of addiction.[7] These glutamatergic neurons, originating in the PFC, Hip, and VTA, project into the NAc. Furthermore, GABAergic neurons within the NAc and cholinergic neurons in the laterodorsal tegmental nucleus activate dopaminergic neurons, initially projecting into the VTA and subsequently into NAc.[7] The NAc acts as an integrative hub, receiving dopaminergic inputs from the VTA and glutamatergic inputs from the PFC.[20] Prolonged exposure to drugs induces alterations in synaptic plasticity, inducing a persistent and functionally rigid form of drug memory.[20] These metaplastic changes in the NAc, attributed to glutamate transmission, manifest themselves in an elevated AMPA/NMDA ratio. Consequently, this increased ratio contributes to an increased proclivity for drug-seeking relapse, even after drug withdrawal and cessation of drug-taking behavior.[20]

Figure 1 delineates the interaction among brain structures and neurotransmitters involved in recognizing rewards, constituting the reward circuit.[21,22] As depicted in Figure 1, it becomes apparent that dopaminergic and glutamatergic neurons play a synergistic role in the addiction process.[23] Another important aspect is the pivotal role

MAIN POINTS

- *To understand the mechanism of action of substance and behavioral addiction.*
- *To understand the mechanism of action of various neurotransmitters that play a crucial role in reward and reinforcement.*
- *To understand the current treatment options for addiction.*
- *To understand the common link emerging from various forms of addiction.*
- *To explore a treatment option that would not only treat the acute phase of addiction but also help in maintaining abstinence, which is potentially safe and feasible.*

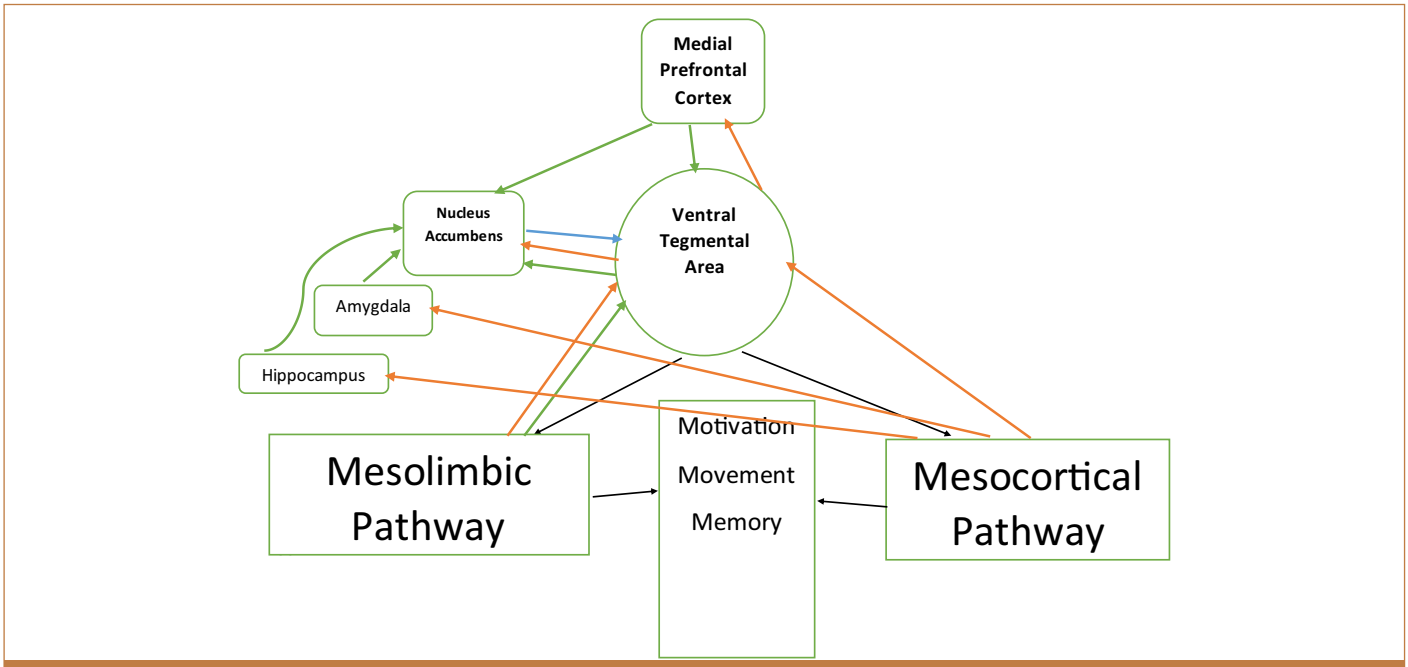

Figure 1. Reward circuit.

of the VTA and the NAc in the reward mechanism, serving as prominent sites for dopaminergic and glutamatergic projections.[23]

Cocaine and Amphetamine Addiction

In the context of cocaine and amphetamine addiction, a notable neurochemical phenomenon involves a significant release of dopamine from the VTA and the NAc, facilitated by the receptors of the glutamate VGLUT2. This mechanism results in enhanced dopamine neurotransmission within the striatum and simultaneously impedes the function of the dopamine transporter (DAT), thus inhibiting dopamine reuptake.[24] Furthermore, these substances also exert their influence on norepinephrine and serotonin transporters, denoted as NET and SERT, respectively.[3]

Opioids (Morphine and Heroin)

Opioid receptors, comprising the Mu opioid receptor (MOP-r), Kappa opioid receptor (KOP-r), and Delta opioid receptor (DOP-r), and their associated opioid neuropeptide systems, which include Proopiomelanocortin/Beta-endorphin (POMC/β-endorphin), dynorphins, and enkephalins, play a crucial role in opioid addiction.[3] The initial rewarding effects of opioids, including prescription pain medications such as oxycodone, hydrocodone, and oxymorphone, acting on MOP-r, involve the projection of Gamma-Aminobutyric Acid (GABA)ergic neurons in the mesolimbic and mesostriatal dopaminergic pathways to the NAc and thalamus (Figure 1), resulting in increased dopamine levels.[3] Furthermore, opioid addiction triggers a burst of firing of dopaminergic neurons from the VTA that project onto the NAc through glutamate VGLUT2, leading to increased dopamine neurotransmission. In this context, dopamine and glutamate act as co-releasing neurotransmitters.[24] At more advanced stages, with persistent reinforcement, the mesolimbic pathway undergoes functional plasticity, resulting in the development of dependence and withdrawal. Avoidance of withdrawal symptoms serves as a negative reinforcement, increasing the temptation to continue using the agonist MOP-r.[3]

Alcohol

Alcohol dependence induces up-regulation of dopamine neurons in the VTA, projecting onto the NAc, thereby eliciting an increase in dopamine release through glutamate vesicular VGLUT2.[24] Additionally, alcohol impacts GABAergic neurons by increasing GABA release. This modulation is accomplished through the inhibition of presynaptic GABA-B receptors and the positive allosteric modulation of postsynaptic GABA-A receptors, particularly those housing δ subunits.[2] Furthermore, beyond dopaminergic systems, the MOP-r system, involving β-endorphin and enkephalins as primary endogenous ligands, emerges as a discernible mediator of reward from alcohol.[3]

Nicotine

Upon inhalation of cigarette smoke or the consumption of tobacco products, nicotine is introduced into the lungs, absorbed into the pulmonary venous circulation, and subsequently enters the arterial circulation.[25] Nicotine molecules quickly cross the blood–brain barrier, gain entry into the central nervous system, and bind to the nicotine acetylcholine receptor (nAChR).[25] The reinforcement effects mediated by glutamate[26] and GABAergic neurons involve the interaction of these neurons with nicotinic cholinergic receptors, specifically nAChR, stimulating the α4β2 receptor and instigating the release of acetylcholine and dopamine.[27] Consequently, in response to nicotine, there is an acute elevation in extracellular dopamine levels in the NAc, and nAChR projects dopaminergic neurons onto the VTA, inducing intense pleasure and a sense of relief.[3] Furthermore, during nicotine withdrawal, there is a reduction in extracellular dopamine levels, creating a window of opportunity for potential treatment modalities.[3] This underscores the importance of bupropion, which exerts inhibitory activity against the DAT, leading to increased extracellular dopamine levels, thus facilitating long-term abstinence.[3]

Cannabis

The brain produces its own neurotransmitters that resemble cannabis, i.e., anandamide and 2-arachidonoylglycerol (2-AG).[2] These

neurotransmitters, along with cannabinoid 1 and 2 receptors (CB1 and CB2), constitute the endocannabinoid system. The CB1 and CB2 receptors are particularly abundant in the brain, particularly CB1.[2] Cannabinoid 1 receptors play a role in regulating the release of other neurotransmitters, including glutamate, GABA, and dopamine.[28] Along the mesocorticolimbic pathway, which encompasses the PFC, the Hip, and the NAc, numerous CB1 receptors are found, influencing motivational and rewarding processes.[28] In contrast, CB2 receptors are predominantly located in the periphery, primarily in immune cells.[2] These receptors exhibit high binding efficacy with 2-AG and low binding efficacy with anandamide.[2]

Upon consumption of cannabis, clinically significant components such as tetrahydrocannabinol and cannabidiol interact with the receptors CB1 and CB2, resulting in the release of psychoactive properties,[2] which alter the motivational and rewarding processes mediated by the CB1 receptors by inhibiting the release of classic neurotransmitters, i.e., anandamide and 2-AG.[28] With prolonged cannabis use, the risk of hallucinations, delusions, anxiety, and memory impairment increases. Furthermore, long-term cannabis consumption, particularly among heavy users, can lead to the development of an "amotivational syndrome," characterized by reduced drive and ambition, shortened attention span, impaired judgement, increased distractibility, decreased communication skills, strained interpersonal relationships, and feelings of depersonalization.[2]

Hypersexuality

The 11th revision of the International Classification of Diseases (ICD-11) has formally incorporated compulsive sexual behavior disorder (CSBD) into the spectrum of addictive disorders. Compulsive sexual behavior disorder is defined by a persistent inability to control intense and repetitive sexual impulses or urges, culminating in compulsive sexual behavior that becomes the predominant focus of an individual's life. This leads to neglect of health, personal care, and a wide range of other interests, activities, and responsibilities. Despite numerous unsuccessful attempts to curtail this compulsive behavior, CSBD individuals persist in their actions, even when faced with adverse consequences or obtaining minimal satisfaction. Furthermore, frontal lobe dysfunction is implicated in CSBD, adversely affecting decision-making capabilities, diminishing inhibitory control over sexual functioning, and impairing judgment, thus fostering sexually disinhibited behavior.[29] This dysfunction can manifest in various clinical conditions, including Kleine–Levin syndrome, Kluver–Bucy syndrome, and dementia.[29] In instances of hypersexual behavior, stimulation of dopamine neurons in the VTA projected onto the NAc is accompanied by repetitive glutamatergic projection, instigating increased activity in the dorsolateral prefrontal cortex, ventral striatum, anterior dorsal cingulate cortex, and amygdala.[6]

Gambling and Internet Gaming

Gambling and internet gaming exhibit many similarities to substance abuse disorders and share common characteristics such as "repeated unsuccessful attempts to stop despite adverse consequences, tolerance, psychological withdrawal (when not "indulging"), and relief when reinitiated."[2] The activation of the mesolimbic dopamine reward pathway (Figure 1) can lead to the development of dependency on gambling and internet gaming in some individuals.[2] This process involves stimulation of both the dopaminergic and endogenous opioid systems.[3]

Current Pharmacological Treatment

Drawing from the neurobiology of addiction outlined earlier, it is well established that addiction manifests itself as a relapsing condition.[3] Furthermore, people grappling with two or more concurrent addictions exhibit a heightened propensity for chronicity and a diminished likelihood of achieving complete recovery.[30] While short-term relief from withdrawal symptoms through appropriate pharmacological interventions does not ensure sustained abstinence from addiction,[3] this section primarily delves into treatment modalities aimed at maintaining abstinence and acting as preventive measures against relapse. The exploration commences by scrutinizing existing psychological and pharmacological treatments tailored to specific substance abuse and dependence. Given the shared neurobiological underpinnings of addiction, particularly those involving dopamine and glutamate neurotransmitter projections, attention is directed towards medications with the potential to function as maintenance treatment in various types of addictions.

Cocaine and Amphetamine

The main focus has been on medications that target the dopamine, norepinephrine, and glutamate neurotransmitter systems. Examples of such medications include modafinil, disulfiram, methylphenidate, and the opioid antagonist naltrexone.[3] However, it is important to note that none of these medications have been approved for the treatment of stimulant addiction.

Opioids (Morphine and Heroin)

The primary approach to managing opioid addiction centers on effective withdrawal management, typically employing opioid agonists such as methadone and buprenorphine.[2] Methadone, which acts as a full agonist at MOP-r with weak NMDA antagonist properties,[3] demonstrates efficacy in alleviating withdrawal symptoms when administered regularly in a clinic and may be especially suitable for individuals with a long history of heroin consumption.[31] Buprenorphine, a partial agonist at MOP-r, effectively treats milder withdrawal symptoms and allows home treatment through sublingual administration,[2] with extended-release injection formulations available as weekly and monthly options.[31] Naloxone, an opioid antagonist administered intramuscularly, has the potential to induce withdrawal symptoms due to its high bioavailability; therefore, a sublingual combination of buprenorphine and naloxone (in a 4:1 ratio) has been developed to mitigate adverse effects by exhibiting a synergistic effect.[31]

Alcohol

Given the impact of alcohol on opioid synapses, clinical intervention involves the use of MOP-r antagonists, specifically naltrexone or nalmefene, to block the euphoria or "high" associated with heavy drinking. Naltrexone can be administered orally or by a monthly long-acting injection.[2] Acamprosate, an NMDA antagonist and GABA agonist, serves as an alcohol substitute during withdrawal.[2] It is usually prescribed for up to 6 months and extended, if beneficial, for up to 12 months and can be used off-label if needed for longer durations.[32] Disulfiram, an irreversible inhibitor of the liver enzyme aldehyde dehydrogenase, impedes alcohol metabolism, resulting in the accumulation of toxic acetaldehyde and adverse effects such as flushing, nausea, vomiting, and hypotension.[2] However, due to poor compliance related to adverse reactions, disulfiram is currently underutilized.[2]

Nicotine

The presence of 20 cigarettes in a pack corresponds to the duration of desensitization of the α4β2 nicotinic receptor, which occurs after finishing one cigarette and lasts approximately 45 minutes.[2] This cycle, aligning with the pleasure experienced at the beginning, requires around 20 cigarettes for individuals awake for 16 hours, explaining the standard pack size of "20 cigarettes."[2]

Treatment aims to maintain desensitization of the nicotinic receptor, achievable through nicotine replacement therapy (NRT) in the form of gums, lozenges, nasal sprays, inhalers, and transdermal patches.[33] Nicotine replacement therapy delivery methods do not replicate the high dopamine supply to the brain obtained from smoking.[2] Alternatively, bupropion, a norepinephrine and dopamine reuptake inhibitor, increases extracellular dopamine levels and reduces craving.[2] Varenicline, a selective partial agonist in nAChR, including the α4β2 receptor, maintains a moderate dopamine supply, minimizing craving and withdrawal symptoms, and supporting smoking cessation.[25] According to the NICE Guidelines (2023), the duration of bupropion treatment is 12 weeks, while the maximum duration of varenicline is 24 weeks.[33]

Hypersexuality

No specific pharmacological treatment is approved for hypersexual behavior, leading to off-label prescriptions as common practice.[29] SSRIs (Selective serotonin re-uptake inhibitors), despite being off-label, are frequently prescribed due to their libido-reducing side effects, with applications noted in treating hypersexual behavior and sexually inhibited behavior in dementia.[29] Naltrexone, also off-label, is used for its ability to block dopamine release in the NAc.[29]

Gambling

Limited evidence exists for the pharmacological treatment of compulsive gambling. A 2018 case series by Ward, Smith, and Bowden-Jones, although with a small sample size (n = 14), demonstrated the efficacy of an 8-week Naltrexone treatment in addressing pathological gambling. Encouragingly, individuals maintained abstinence from gambling 6 months after discontinuation of naltrexone.[34]

Proposed Pharmacological Treatment

Based on the neurobiology and treatment of addiction as mentioned above, our brain has the ability to generate its own neurotransmitters, which can stimulate the reward process. Drug abuse also contributes to the projection of these neurotransmitters onto the structure of the brain, which plays an important role in feeling pleasure. The treatment plan for every type of addiction is focused on increasing the supply of natural neurotransmitters to maintain positive reinforcement, thus reducing the dependency on addictive substances. However, the problem with the agents that are used as replacement therapies is that they either need to be administered under supervision, require regular physical health monitoring due to potential side effects, or have limits for the duration of treatment. Therefore, further research is required to focus on a maintenance treatment that does not require intensive monitoring and would eventually improve compliance.

Glutamatergic neurons in the VTA expressing VGLUT2 not only project to the limbic and cortical regions, but also excite neighboring dopaminergic neurons.[12] Cocaine consumption activates both presynaptic and postsynaptic dopamine receptors, consequently increasing glutamate transmission through NMDA and AMPA receptors.[26] Nicotine enhances glutamate projection by binding to alpha-7 Nicotinic Acetylcholine Receptors (α7 nAChR) located at the presynaptic glutamate terminals.[26] Furthermore, the consumption of alcohol, opioids, or heroin leads to increased glutamate release by inhibiting GABA receptors, subsequently inhibiting presynaptic glutamate terminals.[26] Similarly, CB1 is involved in the regulation of neurotransmitter releases, including glutamate, GABA, and dopamine.[28] Consequently, most drugs of abuse interact directly or indirectly with glutamate receptors.[26] The synergistic effect of glutamate and dopamine neurotransmitters plays a pivotal role in the development of pathological neuroplasticity in the mesolimbic system, contributing to compulsive substance consumption.[16] These observations prompt an exploration of the kynurenine pathway.

The Kynurenine Pathway

The metabolic degradation of the amino acid tryptophan initiates kynurenine pathway (KP).[35] The action of Indolamine 2,3-dioxygenase with tryptophan 2,3-dioxygenase (TDO2) leads to the formation of kynurenine (KYN).[37] Kynurenine is then broken down into 2 compounds of clinical significance. With the action of Kynurenine 3-monooxygenase, a neurotoxic substance called quinolinic acid (QA) is formed, and with the help of Kynurenine aminotransferase, a neuroprotective substance called Kynurenine acid (KYNA).[35] Quinolinic acid interacts with the NMDA receptor complex, leading to excitotoxic neuronal cell loss.[35] Kynurenine acid is an endogenous NMDA receptor antagonist, an agonist of the Aryl hydrocarbon receptor, and a noncompetitive antagonist of nAChR that acts on α7 nAChR.[35] KYNA is the compound of significance in addiction as its derivatives, glucosamine KYNA, 4-chloro KYNA, and 7-chloro KYNA, act on the glutamate receptor, which is transported across the blood–brain barrier and has an antagonistic action on NMDA, blocking glutamate release.[35] Furthermore, it has an additional antagonistic action on α7 nAChR, which is located at the terminals of the mesolimbic pathway.[35] α7 nAChR activates the dopaminergic neurons of VTA and enhances the release of dopamine in NAc.[35] Therefore, the natural synthesis of KYNA in the brain can potentially be used to break the synergistic effect of glutamate and dopamine by blocking glutamate release and increasing dopamine release, enabling the individual to feel reward/satisfaction without the need to consume an addictive substance. However, there is a natural hurdle that prevents KYNA from being used for therapeutic benefit, which is where we need to understand the role of QA. Quinolinic acid, due to its neurotoxic properties, overstimulates the NMDA receptor complex, leading to nerve cell breakdown and is also involved in the pathogenesis of neurodegenerative disorders, including Alzheimer's disease.[36]

Memantine and Galantamine

Memantine is a noncompetitive NMDA receptor antagonist,[36] and the administration of memantine significantly reduces the effect of QA on the brain while actively targeting KYNA.[36] Galantamine, is an acetylcholinesterase inhibitor and nicotinic receptor agonist,[25] and both memantine and galantamine are currently indicated in the treatment of dementia.[37] However, the combination of memantine and galantamine can activate KYNA and produce a dual action.[36] With memantine significantly reducing the effect of QA, it plays a synergistic role with KYNA, resulting in antagonism of the NMDA receptor.[36] Galantamine, which not only allosterically binds to the

α4β2 subunit of the nicotinic receptor (25 is also a α7 nAChR antagonist.[35] Since dopamine is projected from VTA to NAc with the help of glutamate and acetylcholine receptors, the combination of memantine and galantamine can potentially be used in the treatment of addiction. The action of memantine is similar to that of acamprosate in the treatment of alcohol dependence and methadone, which is a weak NMDA antagonist used in the treatment of opioid dependence. Furthermore, the action of galantamine is similar to that of varenicline in the treatment of nicotine addiction. Therefore, there is a strong indication for the potential beneficial effects of combining memantine and galantamine.

In current clinical practice, memantine and galantamine have been widely used in combination for the treatment of dementia.[37] The advantage of using both together is their long-term safety profile. Memantine, like galantamine, does not require long-term monitoring.[38,39] Therefore, unlike other addiction medications that require intensive supervised monitoring due to their side effect profile (as mentioned in the treatment section), memantine and galantamine are relatively safe to prescribe for long-term use. A study by Ashare et al[40] showed that repeated galantamine treatment significantly affected smoking behavior compared to placebo by reducing cigarette use per day by 12% during the 2-week trial period compared to a 7% reduction in the placebo group. A study by Krishnan-Sarin et al[41] showed that combined treatment with naltrexone and memantine produced a significant reduction in drinking and craving compared to treatment with naltrexone alone ($P < .01$). A literature review by Sani et al[42] looked into the role of memantine in the treatment of various mental health disorders other than dementia. They identified a study by Grant et al[43] in which 29 participants who completed the 10-week course of memantine (dose ranging from 10 to 30 mg/day) showed a decrease in the Yale-Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-Y-BOCS) scores from a mean of 22 ± 4 at baseline to 9 ± 7 at the end of the study ($P < .001$). Memantine helped reduce impulsivity to gambling and also improved cognitive flexibility.[43] A higher dose of memantine (20 mg/day), reduced alcohol craving and produced similar sedative, stimulant, and euphoric effects compared to ethanol.[42]

Therefore, based on similar mechanisms of action and similar receptor targets in the treatment of all types of substance and behavioral addiction, we propose the combination of memantine and galantamine as a long-term maintenance treatment in addictive behavior since they target glutamate and dopamine and have a favorable side effect profile. One major limitation in support of this treatment is the limited research around this combination treatment and KP. The few studies that have been conducted exploring the use of memantine and galantamine in combination had small sample sizes and were related to their use in the treatment of dementia rather than addiction.[36] Therefore, more studies are required to understand the long-term outcomes of memantine and galantamine and their potential to be used as a common treatment for any type of addiction.

Concluding Insights and Future Horizons

Addressing addiction poses significant challenges, mainly attributed to the intricate nature of the reinforcement process rather than the reward process, increasing the risk of relapse. This reinforcing mechanism manifests itself similarly across various types of addiction, be it substance-related or behavioral. In light of this, we propose a potential avenue for consideration in addiction maintenance treatment: the combined use of memantine and galantamine. This combination exhibits action on glutamate and cholinergic receptors, influencing dopamine pathways to maintain the reinforcement effect independently of other substances. However, a comprehensive understanding of its potential efficacy requires further investigation through longitudinal studies conducted with larger sample sizes.

However, it is imperative to emphasize that medication alone does not offer a holistic solution to addiction management. A biopsychosocial approach emerges as pivotal, producing more favorable outcomes when pharmacological, psychological, and social interventions are simultaneously implemented. This synergy of approaches addresses the multifaceted dimensions of addiction, offering a more comprehensive and effective strategy for intervention and long-term recovery.

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