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REVIEW ARTICLE

Critical View on the Usage of Ribavirin in Already Existing Psychostimulant-Use Disorder

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Abstract: Substance-use disorder represents a frequently hidden non-communicable chronic disease. Patients with intravenous drug addiction are at high risk of direct exposure to a variety of viral infections and are considered to be the largest subpopulation infected with the hepatitis C virus. Ribavirin is a synthetic nucleoside analog that has been used as an integral component of hepatitis C therapy. However, ribavirin medication is quite often associated with pronounced psychiatric adverse effects. It is not well understood to what extent ribavirin *per se* contributes to changes in drug-related neurobehavioral disturbances, especially in the case of psychostimulant drugs, such as amphetamine. It is now well-known that repeated amphetamine usage produces psychosis in humans and behavioral sensitization in animals. On the other hand, ribavirin has an affinity for adenosine A1 receptors that antagonistically modulate the activity of dopamine D1 receptors, which play a critical role in the development of behavioral sensitization. This review will focus on the current knowledge of neurochemical/neurobiological changes that exist in the psychostimulant drug-addicted brain itself and the antipsychotic-like efficiency of adenosine agonists. Particular attention will be paid to the potential side effects of ribavirin therapy, and the opportunities and challenges related to its application in already existing psychostimulant-use disorder.

Keywords: Ribavirin, adenosine, amphetamine, brain, antipsychotic efficiency, physiological response.

1. INTRODUCTION

The drug in use is under the continuous supervision of clinicians and researchers responsible for monitoring and examining its effects, and sometimes it can lead to the discovery of its new applications and/or side effects. An introduction of a new drug to the market is a prolonged and expensive process which implies its discovery, development, preclinical and clinical testing, and approval by the national regulatory authority. Discovering new uses for an old drug, *i.e.*, drug repurposing or drug repositioning, is a highly efficient, low-cost, and a safe approach to find new or to extend current therapeutic purposes of an existing drug [1, 2]. Conversely, detection of the side effects of a drug, once it is approved for use, leads to its application with great caution or even more complete avoidance in some conditions.

Ribavirin is a synthetic nucleoside analog that has been used as an antiviral drug for many years [3-13]. It has been revealed that ribavirin treatment causes side effects, such as depression, anxiety, psychosis, cognitive impairment, and body weight loss [14-18], which significantly limit or detain its application in patients with psychiatric disorders and/or substance abuse. Although it is typically used as an antiviral drug, it can also modulate behavioral response induced by amphetamine (AMPH) [19-21], implying its possible application in counteracting psychostimulant-induced effects. These findings indicate the importance of further monitoring and examining the effects of ribavirin in these conditions in order to determine the benefits and adverse consequences of its treatment.

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2. SUBSTANCE-USE DISORDER AS A NON-COMMUNICABLE CHRONIC DISEASE

Non-communicable diseases are chronic diseases characterized by long duration and slow progression. They affect people of all ages and are the leading cause of death worldwide. According to the global status report released by the World Health Organization [22], they were responsible for 38 million (68%) of the world's 56 million deaths in 2012. Unhealthy diets, physical inactivity, exposure to tobacco smoke, or harmful use of alcohol are four main risks contributing to non-communicable diseases [23-26]. The most common are cardiovascular diseases such as, heart attacks and stroke, cancers, chronic respiratory diseases such as, chronic obstructive pulmonary disease and asthma, and diabetes.

The substance-use disorder is one of the frequently hidden and neglected non-communicable diseases despite causing a considerable health burden [27]. In many countries, it is separated from general healthcare with resources that are not adequate for the burden. Treatment rates for people with substance-use disorders are low and slow, with treatment gaps of more than 90% in developing countries [28-30].

The substance-use disorder is a medical condition related to repeated use of a substance that leads to severe health and social problems, including addiction [31]. The term "substance" refers to psychoactive compounds, such as nicotine, alcohol, cannabinoids, hallucinogens, opioids, sedatives, hypnotics or anxiolytics, as well as stimulants. These compounds can be legal (*e.g.*, nicotine), illegal (*e.g.*, heroin and cocaine), or prescribed for medical purposes (*e.g.*, opioids), and they have one thing common that is, their use produces feelings of pleasure. Substance abuse and drug dependence produce significant and lasting changes in the brain chemistry and function [32-36]. Due to long-term and severe consequences, which could be caused by substance abuse, there is a generally accepted

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view that substance-use disorder represents a chronic disease [37]. As the leading cause of life with a disability, substance-use disorder could be one of the biggest health problems of future.

3. PSYCHOSTIMULANT ADDICTION

Stimulants are known to alleviate fatigue, increase vigilance, and generally increase work output [38]. It has been suggested that their use might be motivated, at least in part, by a desire to relieve behavioral and cognitive deficits [39, 40]. AMPH-type stimulants are the fastest rising drugs of abuse worldwide, ranking the second most commonly used illicit drugs after cannabis, followed by cocaine and opiates [41, 42]. North America is the second to the East and Southeast Asia, in the prevalence of AMPH users with an estimated 3.92 million current users in North America [42].

3.1. Amphetamine-A Brief Historical Overview

AMPH was first synthesized by a Romanian chemist named Lazar Edeleanu at the University of Berlin in 1887. Biochemist Gordon Alles re-synthesized the drug in the 1920s, subsequently discovering its psychoactive effects. Searching for a decongestant and bronchodilator as a substitute for ephedrine, Gordon Alles discovered the physiological activity of beta-phenyl-isopropylamine, known as AMPH. Although AMPH was thought to be a human invention, the compound was found in 1997, along with methamphetamine, nicotine, and mescaline, within two species of Texas acacia bushes [43, 44].

In the early days of scientific drug discovery, researchers routinely experimented on themselves and familiarity with a compound made them the best observers of its effects. On June 3, 1929, a twenty-seven-year-old Gordon Alles took an injection of a chemical he had recently created (preliminary data known from guinea pig tests) and his doctor friend, Hyman Miller, discovered the changes which included a blood pressure rise within 10 min, dry and clear nose, a "sense of well-being" soon after, normal blood pressure 8 h after taking the drug, increased talkativeness and good spirit, and a "rather sleepless night" [45]. Alles began sharing the drug with a group of doctors and researchers for experimental use and published his first clinical results with the substance in 1930 [46]. He protected his intellectual property and received a patent: a 1932 U.S. patent that declared him the inventor of amphetamine sulfate and amphetamine hydrochloride, recognizedhim as the discoverer of their medicinal values. Meanwhile, the Philadelphia firm Smith, Kline and French (SKF) investigated the base form of AMPH and patented it in 1933 as the Benzedrine Inhaler, a capped tube containing 325 mg of oily AMPH base (for congestion, one was meant to inhale AMPH vapor every hour as needed; [47]). There was no legal category of prescription drugs in the 1930s, and Benzedrine Inhaler was advertised for sale without a prescription [48].

In the early 1937, the new drug, Benzedrine sulfate, appeared in the form of a pill. In 1936, researchers at the University of Minnesota had given pills to student volunteers to evaluate any psychological effects. The participants realized they could use it to stay awake and study harder. In 1937, psychiatrist Charles Bradley administered Benzedrine sulfate to "problem" children in an attempt to alleviate headaches and noticed an unexpected effect upon the behavior of the children, *i.e.*, improved school performance, social interactions, and emotional responses [49]. It was noted for the first time that AMPHs could produce a "paradoxical" relaxing effect in severely disruptive, institutionalized, hyperactive boys [49], which paved the way for their more common medical use in the attention-deficit/hyperactivity disorder (ADHD). The greatest experiment in AMPH-based enhancement came in World War II. By mid-1940, the British and American militaries had begun their investigations of Benzedrine's ability to help combat fatigue and boost the morale of soldiers, and a study by the British War Office discovered a similar use within the German military [50]. As concluded in this excellent review article, the grounds on which armies adopted AMPH had less to do with the science of fatigue than with the drug's mood-altering effects, as judged by military men - increased confidence and aggression, and elevated "morale."

As a molecule with a single chiral center, AMPH exists in two optically active forms, *i.e.*, the dextro- (or *d*-) and levo- (or *l*-) isomers or enantiomers. The *l*-AMPH (Cydril) achieved far less attention than either the racemate (Benzedrine) or *d*-isomer (Dexedrine), although clinical trials conducted in the 1970s demonstrated that both isomers of AMPHs were clinically effective in treating ADHD [51]. Nevertheless, *l*-AMPH produces more cardiovascular and peripheral effects than the *d*-enantiomer. Both AMPH isomers are equally potent noradrenaline releasers, but *d*-isomer is about three-fold more potent than *l*-isomer as a dopamine releaser, which points to dopamine as the primary neurochemical mediator of AMPH's stimulant properties [51-53].

By 1940, AMPH was already known to have abuse potential, gaining popularity among nonmedical users, as the "pep pill" in the United States and "the confidence drug" in Britain [50]. Benzedrine's ability to improve mood and relieve feelings of monotony made it susceptible to abuse. After World War II, much of the stocks got into the "black market" and in the 1950s, AMPH abuse became evident [51]. By 1980, most of the countries that regulate drug use had severely restricted the legal use of AMPHs, but the number of prescriptions and prescription abuse continued to grow, particularly in North America [54]. In the United States and internationally, AMPH is classified as a Schedule II drug - accepted medical use, but tightly monitored due to its potential for abuse that can lead to severe psychological and physiological dependence [54]. Over 95% of pharmaceutical AMPHs are either *d*-isomer or a mixture of *d*- and *l*-isomer salts [54].

3.2. Amphetamine Usage and Side Effects

An essential fact about AMPH is its use as an antidepressant in the 1950s before the discovery of the tricyclic monoamine reuptake inhibitors. When it was noted that a side effect of Benzedrine ingestion was the suppression of appetite, AMPH (especially Dexedrine) became a wildly popular diet drug. By 1962, the Food and Drug Administration (FDA) estimated that 8 billion pills, or an astonishing forty-three per person, were being sold annually [55]. Rasmussen cites evidence that approximately 2 to 3 percent of those prescribed the drug in the 1960s became addicted; since 10 million Americans had been prescribed an AMPH in 1970, this would mean 200,000 to 300,000 addicts [48]. Importantly, in a classic study of that period, Connell from the Institute of Psychiatry reported a group of heavy AMPH users who had become paranoid [56], highlighting the potential psychiatric dangers related to the use of this drug.

Because of their stimulant activity within the central nervous system (CNS; proposed mode of action described below), AMPHs have been examined for the treatment of several disorders, including ADHD (most pharmaceutical AMPH is used in the treatment of ADHD, [54]), daytime sleepiness associated with narcolepsy ([57]; AMPHs produce objective improvement in 65-85% of patients with narcolepsy, [58]), and obesity [59]. Although AMPHs remain among the most effective appetite suppressants by the 1990s, the United States Pharmacopoeia's resource no longer recommended AMPH for treatment of obesity due to the high abuse potential and availability of equally effective appetite-suppressants with lower abuse potential [54]. Furthermore, AMPHs induce euphoria, increase alertness, decrease appetite and fatigue, increase heart rate, blood pressure, and breathing rate, constrict blood vessels, dilate pupils, and release glucose and lipids into the bloodstream [60]; the user has an intense fascination with all his thoughts and activities [61]. The effects may appear within 30 to 40 min and last for 4 to 8 h depending on the formulation (immediate-release or sustained-release formulations), route of administration (orally, snorted, smoked, or injected intravenously), and the dose [54, 60]. To

achieve the most significant pharmacological effect and immediate gratification/pleasure the drug must be delivered into the CNS in the shortest possible time, which causes drug abusers to progress from relatively safe methods of self-administration (*i.e.*, oral ingestion) onto more dangerous routes of administration (such as intravenous injection). The kinetics of AMPH, when taken orally, makes it less rewarding (pleasurable) than cocaine or methamphetamine, while the intravenous use of AMPH and other stimulants, although more pleasurable, still poses significant safety risks to the individuals indulging in this practice [51]. Chronic use of AMPH-like stimulants can culminate in addiction (the loss of control over drug taking) and psychosis with tolerance and sensitization (depending on the dose and the interval between the drug treatments), which is better explained within the next subheading. Special attention was paid to appetite suppression (subheading 3.4.) as a reduction in body weight due to continuous AMPH use may lead to malnutrition and consequently to decreased resistance to diseases.

The development of tamper-deterrent AMPH formulations has been a substantial objective of the pharmaceutical industry to prevent this type of abuse. Several new once-daily AMPH-containing prescription drugs with a high degree of tamper deterrence have emerged (*e.g.*, Adderrall XR). Besides, lisdexamfetamine as a prodrug of AMPH is the next step in the reduction of brain drug concentration, thereby further reducing the pleasurable effects of the AMPH [51].

Importantly, many of the behavioral effects of AMPHs that have been observed in humans can be demonstrated in experimental animals. These include arousal, hyperactivity, stereotypic perseverative movements, psychomotor depression, cognitive impairment, hallucinatory-like behaviors, and chronic self-administration [51, 54]. Animal studies have been crucial in understanding the biology and pathophysiology of drug addiction and substance abuse because, in contrast to clinical studies, the subject population can be controlled for variables more efficiently, thus better reflecting the ability of the drugs to control the animal's behavior [62]. Animal studies have demonstrated that some of the typical behaviors associated with drug abuse in humans involve biological processes common to mammalian species [63].

3.3. The Phenomenon of Behavioral Sensitization

Studies from several disciplines support the concept that while chronic, continuous stimulation with agents acting directly (apomorphine) or indirectly (AMPH, cocaine) at dopaminergic receptors is often associated with the development of tolerance, intermittent stimulation, under some circumstances, may have the opposite effect and be associated with sensitization or reverse tolerance [64]. These findings suggest that the interval between stimuli is vital in determining subsequent responsiveness. In humans, it is well documented that the chronic use of AMPH-like stimulants elicits a progressive augmentation in paranoid behaviors that can culminate in psychosis [65]. Tolerance after continuous administration has been described as well, initiating increases in dosage and frequency of administration to achieve a specific mental state [61]. Interestingly, evidence of sensitization of behavioral effects in healthy adults after three identical administrations of 0.25 mg/kg of AMPH 48 h apart has been reported [66].

Behavioral sensitization has been well characterized for psychomotor stimulants, and refers to the progressive enhancement of behavioral responses to drugs following their repeated intermittent administration [65, 67, 68]. The development of these maintained behavioral adaptations parallels the progressive and sustained enhancement of drug-craving and psychotic behaviors displayed by addicts only after repeated administration [69, 70]. Increased activity of the ventral tegmental area (VTA; A10 dopamine neurons) is crucial for the initiation, while ventral striatal adaptations (enhanced sensitivity of dopamine D1 receptor, enhancement of dopamine release, increased activity of Ca^{2+}/calmodulin-dependent protein kinase IIα (CaMKIIα, a biochemical sensor of synaptic activity)) play a role in the expression of behavioral sensitization (Fig. **1**) [71-73].

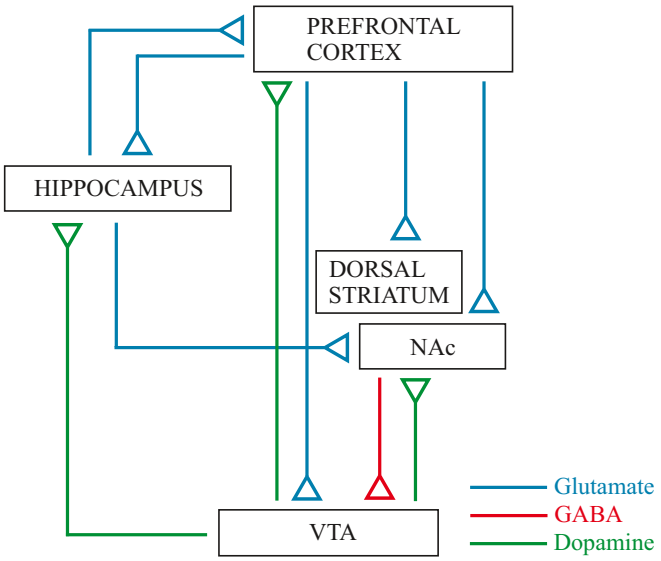

Fig. (1). Schematic presentation of neurocircuits associated with behavioral sensitization and drug addiction (for details see section 3.3.). Abbreviations: NAc - nucleus accumbens; VTA - ventral tegmental area.

The findings by Cador *et al.* [74] showed that AMPH action solely at the level of dopamine cell bodies in the VTA is necessary and sufficient to promote changes subserving behavioral sensitization, which can be later revealed by an AMPH action at the level of dopamine terminals in the nucleus accumbens. On the contrary, the sole AMPH action at the level of the nucleus accumbens is not sufficient to promote these changes, but it is necessary to allow their expression. These findings argue for a complete dissociation of neuroanatomical substrates, which mediate the induction and expression of behavioral sensitization to AMPH [74].

The phenomenon of behavioral sensitization provides a reasonably good rationale for establishing a model of AMPH psychosis (while the AMPH neurotoxicity syndrome does not). This rationale goes hand in hand with the factual knowledge that the daily administration of only 0.3 - 1.2 mg/kg of AMPH can lead to AMPH-induced psychosis in healthy subjects [67]. Overall, low doses of stimulants cause increased arousal, attention, and cognitive enhancement (an inverted U-shaped dose-effect curve); moderate doses can lead to feelings of euphoria and power, as well as addiction and cognitive impairment; and very high doses lead to psychosis and circulatory collapse [75]. The ability of low-dose AMPH (that does not substantially impact locomotor activity) to maintain wakefulness and increase alertness has long been exploited, contributing to the widespread use (in the treatment of ADHD and narcolepsy) and abuse of these drugs [76]. For healthy, adult humans, doses in the 0.07 - 0.40 mg/kg range, can be considered to be those that generally produce subjective effects consistently different from placebo, enhance mood as assessed by a variety of scales, and improve performance on a variety of physical and cognitive tasks, without inducing dysphoric reactions or disrupting task performance in most individuals [77]. The lowest reported dose of AMPH that produces sensitization of vigor and euphoria in healthy adults is 0.25 mg/kg [66].

It should be noted that some findings suggest that in patients, the effects of low-dose AMPH administration are negligible and could be used to enhance recovery from motor and language deficits after a stroke [78, 79]. These discoveries overall questioned

prolonged usage of low AMPH doses (that presumably improve mood) in adults, and this has been recognized as a current research priority, especially considering medical/prescription usage of low doses [54]. Much remained unclear about the mechanisms and nature of the dose-response relationship between the use of AMPH and psychotic response [80].

Locomotor sensitization gained much interest in previous work mainly because it is believed to be related to incentive-sensitization or enhanced "drug wanting" [69, 70], *i.e.*, rats that develop locomotor sensitization subsequently show enhanced self-administration of psychomotor stimulants [71]. The mesolimbic and mesostriatal dopamine pathways are involved in locomotion and stereotypy, respectively [81, 82] with the mesolimbic dopamine system being recognized as more responsive than extrapyramidal dopamine system to repeated intermittent exposure to moderately low doses of AMPH (0.5 - 2 mg/kg; [83]). Previous findings that suggested mediation of certain forms of AMPH-induced behaviors by different neuronal circuits (*i.e.*, a strong coupling between locomotion elicited by low and moderate doses of AMPH and the level of metabolic activity in the nucleus accumbens, as well as between stereotypic behavior elicited by high and moderate doses of AMPH and an increase in glucose utilization in the extrapyramidal system) should be noted as well [84]. Literature indicates that in a rodent model, the sensitization to the rewarding effects of AMPH could be produced by doses less than 1.0 mg/kg, ranging up to 10 mg/kg, with typical injection frequencies of one or two times daily for 1 - 2 weeks [83]. However, although all doses of AMPH increased endogenous level of striatal dopamine they differentially influence dopamine synthesis, *i.e.*, high doses of AMPH (5 - 10 mg/kg) decreased dopamine synthesis, the dose of 3 mg/kg produces a biphasic response (increase followed by decrease), while low doses (to 2.0 mg/kg) increase dopamine accumulation in the striatum [85, 86].

The dopaminergic system of the midbrain, especially its mesoaccumbens pathway, which mediates the stimulatory effect of psychostimulants on locomotion, has been the focus of research dealing with the neurobiological bases of AMPH-induced behavioral sensitization for a while [65, 67, 87]. Aside from AMPH-induced dopamine release through a dopamine transporter, a more recent study suggests that there might be a non-dopamine transporter-mediated mechanism of dopamine release [87]. This mechanism is mediated through AMPH-induced pronounced, rapid and dose- and time-dependent increase of norepinephrine in the prefrontal cortex, which in turn may alter the firing pattern of dopamine neurons, thus affecting the temporal pattern of dopamine release in the nucleus accumbens [87, 88]. This effect occurs predominantly by reuptake blockade at lower doses and by dopamine release at higher ones [89]. At doses of 2.0 mg/kg and higher, as well as over 1.75 mg/kg, AMPH significantly increases extracellular concentrations of serotonin and acetylcholine, respectively [90, 91]. Therefore, although some reports indicate that single exposure to AMPH (5 mg/kg) is sufficient to induce long-term behavioral, neurochemical, and neuroendocrine sensitization in rats [92], this dose of AMPH belongs to the high dose range that allows specific neurochemical alterations, as discussed above.

3.4. The Appetite Reduction in Response to Amphetamine Usage

The appetite reduction in response to AMPH usage is another essential health problem as continuous use may lead to malnutrition and, consequently, to decreased resistance to diseases. It has been reported that following the drug usage appetite for food is suppressed completely [61]. Anorexigenic effects of AMPH are not fully understood, but there is a view that due to the drug exposure, food does not have reinforcing properties, and therefore, does not serve as an incentive for a learned behavioral compensation [93]. It has been shown that when rats are given repeated injections of AMPH in an environment containing food, they develop tolerance to the initial suppression of feeding; tolerance does not develop when they are given the same number of drug injections in the absence of food [94]. One interpretation of this finding is that rats given AMPH with food gradually learn to suppress stereotyped head movements, which interfere with feeding, while rats given the drug without food have neither the opportunity nor the incentive for such learning [95]. However, some findings pointed out that increased hypophagia was not well correlated with changes in stereotypy and emphasized the importance of a schedule of injections in determining AMPH's effects [96]. Nevertheless, in humans, drug use could take place in complex environments that may modify the pharmacological and behavioral effects of drugs. So far, there is a substantial disagreement regarding which of AMPH's behavioral effects is altered by the presence of food [93]. It has been recognized that the environment can modify the responsiveness to addictive drugs, and that immediate surroundings during drug-taking can alter the behavioral, subjective, and rewarding effects of a given medication, thus influencing the propensity to use the same drug again [97].

The mechanism by which AMPH causes a loss of body weight has been examined in early experimental studies on dogs and humans by Harris *et al.* [98]. The data showed clearly that loss of body weight due to the administration of AMPH is associated with a reduction of voluntary food intake, and that the appetite (or the attitude toward food) returns to normal after the drug administration is discontinued [98]. The dose of 0.14 mg/kg was recognized as effective in appetite suppression in humans, and this dose (9.8 mg/70 kg) has been used extensively in behavioral studies with humans, and is well tolerated [99, 100]. In humans, acute administration of AMPH in the dose range of 10 - 30 mg/70 kg decreased 24-h caloric intake by 24 - 30% [101].

The effect of AMPH on food consumption in rats has been observed as well [102]. Several studies showed that [^{3}H]AMPH binds to receptors in brain tissue, demonstrating the presence of both a low- and a high-affinity saturable stereospecific protein-binding site for AMPH and mazindol (appetite suppressant) on synaptosomal membranes in the hypothalamus and corpus striatum [103, 104]. AMPH acts mainly by blocking the dopamine transporter that inhibits the dopamine reuptake and therefore increases the concentration of dopamine at the synapse, but the mechanism underlying the anorectic response of AMPH is also attributed to its inhibitory effect on hypothalamic neuropeptide Y (NPY), an orexigenic peptide in the brain [105]. It has been shown that adult male Wistar rats receiving 1, 2, or 4 mg/kg AMPH at the beginning of the dark period (in rats, most feeding behaviors took place in the dark phase along with feeding behavior activation) markedly decrease the amount of food intake compared with the control [106]. These authors also showed that AMPH treatment at doses of 2 and 4 mg/kg resulted in a significant decrease in the concentration of hypothalamic NPY that has a pattern of circadian rhythm, with high concentration appearing at the beginning of the dark phase. The proposed mechanism of the action of AMPH administered peripherally in the dose of 1 mg/kg accentuated the role of dopamine and norepinephrine release into the anterolateral hypothalamus as necessary for the suppressive effect of the treatment on feeding behavior [107].

From a clinical perspective, AMPH withdrawal in humans could be related to increased appetite [108], and some findings reported an increased rate of weight gain during the 29-day withdrawal period in AMPH-treated rats relative to saline-treated controls [109]. Other studies also reported that cessation of systemic injection of AMPH (3 mg/kg, for 9 consecutive days) increases food consumption over the course of 30 days, indicating AMPH-induced sensitization of mechanisms involved in reward motivation and suggesting that weight gain following drug cessation in humans could be due to similar mechanisms [110]. Importantly, it has also

been recognized that withdrawal from psychostimulants produces depressive-like symptoms and affects response to natural reinforces [111]. Experimental findings also suggest that inadequate body weight gain could be detected in experimental animals for up to 3 weeks after AMPH administration [112].

3.5. Injection Drug Use and Infectious Diseases

Abuse of AMPHs administered intravenously has become a well-established and extensive form of drug abuse, and it has been suggested that the abuse potential of these drugs, when taken by the intravenous route, is comparable to that of heroin or cocaine [61]. Methamphetamine and AMPH-type stimulant use has increased in the United States in the last 20 years and has been recognized as a risk factor for hepatitis C virus (HCV) infection [113]. When AMPH is taken intravenously, dirty needles and unhygienic conditions may damage the body and cause infections. Importantly, it has been accentuated in the recent studies that substance use (and psychiatric disorders) is common among patients with HCV infection and that there has been a minimal examination of the type of substance use and impact on HCV-related outcomes in the clinical setting [113]. Globally, 71 million people were estimated to be living with HCV infection in 2015, of which 5.6 million (8%) were "currently" injecting drugs [114]. Also, there is a large, undetermined fraction of those with chronic HCV infection that have stopped injecting drugs [115].

Within past years, antiviral treatment of HCV has evolved from pegylated interferon and ribavirin to pegylated interferon and ribavirin with new direct-acting antiviral (DAA) medications, to interferon-free DAA combinations. Some studies suggest that the careful treatment management among addicts treated with directly observed pegylated interferon alfa-2a plus self-administered ribavirin sustained virologic response is comparable to that seen in clinical trials of non-drug users, and the rate of HCV reinfection is low [116]. However, it has been recognized that patients with HCV infection, psychiatric disorders, and/or substance abuse sometimes face significant barriers to antiviral treatment and may complicate tolerance and adherence to antiviral therapies [117]. Moreover, side effects of standard antiviral treatment for HCV infections have been recognized, and include depression, anxiety, psychosis, cognitive impairment, and body weight loss [14-18], which may further complicate its application in HCV-infected patients with psychiatric disorders and/or substance abuse.

4. THE ROLE OF ADENOSINE RECEPTORS IN PSYCHOSTIMULANT ADDICTION

Adenosine has physiological roles and is also involved in pathological processes such as epilepsy, neurodegenerative, and psychiatric disorders [118-121]. It acts as a neuromodulator in the CNS that fine-tunes neuronal activity and is responsible for homeostasis maintenance and prevention of functional and metabolic activation. These effects of adenosine are mediated by activation of Gi/o-/Gq-coupled A1 and A3 or Gs/Golf-coupled A2A and A2B receptors [122]. Extracellular concentrations of adenosine are approximately 30 to 300 nM under physiological conditions [123, 124] and above 1 μM in conditions of seizures, hypoxia, ischemia, electrical stimulation, *etc.* [125, 126]. They are a reflection of the balance between multiple mechanisms that, on the one hand, increase extracellular adenosine level, and on the other hand, promote its uptake and metabolism.

So far, it is determined that adenosine A1 and A2A receptors are highly abundant in the mesolimbic system of the brain, especially in the ventral striatum and nucleus accumbens [127]. Functional manipulation with these receptors has revealed their role in the behavioral effects of several addictive drugs, including reinforcement, sensitization, and withdrawal, as well as the reinstatement of instrumental responding [128, 129]. Pharmacological studies showed that both A1 and A2A agonists inhibit acute AMPH-induced locomotion in intact animals and apomorphine-induced rotation in rats unilaterally lesioned with 6-OHDA [19, 20, 130-133]. A critical role of A1 and A2A receptors in the development of psychostimulant-induced behavioral sensitization has also been recognized [134, 135].

4.1. Adenosine System in Addiction and Psychosis

The adenosine system is the central controller of neurotransmitter systems that are affected in psychostimulant addiction [128, 136, 137]. Therefore, adenosine receptors are of particular interest in the development of therapeutic strategies in counteraction of psychostimulant-induced effects [128]. Indeed, there is increasing evidence of antagonistic interactions between dopamine and adenosine receptors in methamphetamine and cocaine addiction [137, 138]. The importance of the adenosinergic system in these effects, such as disturbed locomotor activity encountered in behavioral sensitization, was definitively confirmed in experiments done on A2A receptor knockout mice. For example, Chen *et al.* [135] reported that there is a selective absence of AMPH-induced behavioral sensitization in A2A knockout mice, thus confirming a critical role of these receptors in the development of psychostimulant-induced behavioral sensitization. Also, some genetic experiments confirmed that variations among the Japanese population in the A2A adenosine receptor (ADORA2A) gene could be a vulnerability factor that increases genetic susceptibility to methamphetamine dependence/psychosis, especially in females and/or in patients using only methamphetamine [138]. In addition to all these genetic pieces of evidence, scientists further confirm that the genetic blockade of A2A receptors induces cognitive impairments and anatomical changes related to psychotic symptoms in mice [139].

On the other hand, there are argumentative suggestions that hypofunction of adenosine signaling may contribute to the pathophysiology of schizophrenia [140]. At least two adenosine depots, striatal and hippocampal, might be implicated in schizophrenia. However, the above mentioned structurally-located adenosine systems show the independent contributions of these two interconnected brain regions in the pathophysiology of schizophrenia, at least in the case of Adk transgenic mice [140]. It is now widely believed that the treatment of schizophrenia relies not only on restoring a dysregulated striatal dopamine and prefrontal cortex glutamate neurotransmission, but adenosine neurotransmission as well [141]. Standard treatments of schizophrenia symptoms rely on drugs that act on the restoration of dysregulated striatal dopamine and prefrontal cortex glutamate neurotransmission - these treatments are usually insufficient to fully cover all the disease symptomatology (*i.e.*, negative and cognitive symptoms) [141]. Keeping in mind that the disruption of adenosine homeostasis in the brain has many behavioral symptoms similar to schizophrenia, and the fact that adenosine interferes with both dopaminergic and glutamatergic neurotransmission, it has been postulated that restoring adenosine concentration within the schizophrenia-related brain areas might have beneficial antipsychotic properties [141]. Also, in quinpirole sensitization-induced obsessive-compulsive disorder (OCD) - model in mice, the administration of an A2A antagonist (istradefylline) alleviated both the quinpirole-induced abnormal OCD behaviors with only short-term administration [142]. Therefore, successful antipsychotic strategies based on the manipulation of the adenosine system of the brain will constitute a new opportunity for therapeutic intervention in psychoses such as schizophrenia and OCD. In this respect, targeting the high-affinity adenosine receptors (A1 and A2A), and the regulatory enzyme adenosine kinase provides the rationale for further development of effective adenosine-based antipsychotic drugs [143].

4.2. Adenosine A1 and A2A Receptors in the Basal Ganglia: Distribution and Function

The basal ganglia represent a substrate for the multiple actions of psychostimulants that, by altering dopaminergic neurotransmission within their distinct pathways, cause behavioral perturbations

[144]. The basal ganglia consist of several interconnected subcortical nuclei, including striatum, globus pallidus (external or lateral segment - GPe and internal or medial segment - GPi), subthalamic nucleus, and substantia nigra [145]. The central component is the striatum, and it is divided into dorsal and ventral sections in primates. The dorsal striatum is composed of the caudate nucleus and the putamen, and it is involved in controlling motor movements and executive functions. The ventral striatum is composed of the nucleus accumbens and the olfactory tubercle, and it is responsible for limbic functions of reward and aversion. The striatum receives excitatory projections from the cortex, thalamus, and limbic areas, and dopaminergic projections from the mesencephalon (Fig. **2**). Striatal outputs are primarily composed of GABAergic medium-sized spiny neurons divided into two equally large subpopulations based on their projections and protein content. One subpopulation projects directly to the output nuclei (substantia nigra pars reticulata and GPi), contains substance P and dynorphin, and is a part of "direct pathway." Another subpopulation projects indirectly to the output nuclei *via* GPe and the subthalamic nucleus contains enkephalin and is a part of the "indirect pathway." The direct pathway projection neurons primarily express dopamine D1 receptors, while those of the indirect pathway mostly express dopamine D2 receptors. The nigrostriatal and mesolimbic dopaminergic pathways represent the major feedback systems within the basal ganglia, and dopamine plays a vital role in the coordination and regulation of the two major output pathways [146]. The most acceptable model of the basal ganglia assumes that the direct and indirect paths have an inhibitory and excitatory effect, respectively, on the neuronal activity of the output structures that tonically inhibit motor activity [145]. In this model, dopamine inhibits the indirect pathway acting on D2 receptors and stimulates direct pathway acting on D1 receptors, resulting in activation of motor behavior.

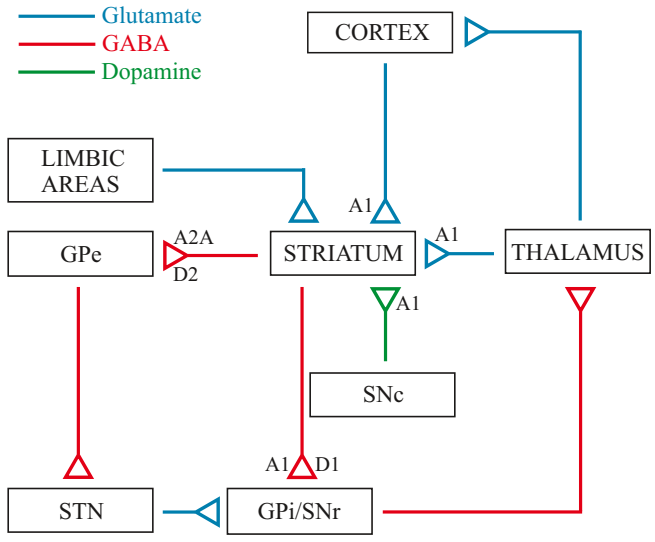

Fig. (2). Schematic presentation of the major afferent/efferent projections of the basal ganglia and distribution of adenosine (**A**) and dopamine (**D**) receptors (for details see section 4.2.). Abbreviations: GPe - external segment of the globus pallidus; GPi - internal segment of the globus pallidus; STN - Subthalamic nucleus; SNr - Substantia nigra pars reticulata; SNc - Substantia nigra pars compacta.

Adenosine A1 receptors are found pre- and postsynaptically [122, 147] in the striatum, globus pallidus, substantia nigra, and nucleus accumbens [147, 148]. Activated by nM concentrations of extracellular adenosine present under physiological conditions [123, 124], they reduce adenylyl cyclase activity and cyclic adenosine monophosphate (cAMP) production, inactivate Q-, P-, and N-type voltage-gated Ca^{2+} channels, and stimulate K^{+} conductance and phosphoinositide metabolism [122, 149, 150] leading to strong inhibition of synaptic transmission. The presence of A1 receptors was confirmed on corticostriatal, thalamostriatal, and nigrostriatal afferents, where they are involved in the depression of glutamatergic and dopaminergic neurotransmission [151-153]. Besides, A1 receptors are co-expressed with D1 receptors on striatonigral-striatoentopenduncular neurons, and their stimulation reduces D1 receptor-mediated GABAergic neurotransmission [154, 155].

Adenosine A2A receptors, located pre- and postsynaptically predominantly in dopamine-rich brain regions including striatum, olfactory tubercle, and nucleus accumbens [156, 157], are tonically activated by endogenous adenosine [158]. Stimulation of A2A receptors increases adenylyl cyclase activity leading to an increase in cAMP level and activation of cAMP-dependent protein kinase, which then phosphorylates and activates numerous receptors, ion channels, phosphodiesterases, and phosphoproteins such as CREB (cAMP response element-binding protein) and DARPP-32 (dopamine and cAMP-regulated phosphoprotein) [157]. Unlike A1 receptors, activation of A2A receptors potentiates P/Q type Ca^{2+} currents [159, 160], resulting in increased synaptic transmission. In the striatum, A2A receptors are co-expressed with D2 receptors on GABA/enkephalin striatopallidal neurons, and their activation interferes with effects mediated by D1 receptors [157].

Adenosine A1 and A2 receptors fulfill important neuromodulatory and homeostatic functions by interacting with dopamine and other neurotransmitters in the brain, which are responsible for motor, emotion, learning, and memory function. A1 receptors play a crucial role in neuroprotection since they decrease glutamate release and hyperpolarize neurons in various pathological conditions [118-121]. Not only can the use of A1 agonists and antagonists aid in brain neuroprotection, but coupling A2A antagonists with activation of A1 receptors might also constitute the more robust neuroprotective strategy based on the adenosine neuromodulatory system [161]. Indeed, balanced activation of inhibitory A1 receptors imposes a tonic brake on excitatory transmission, whereas facilitatory A2A receptors activation selectively engages in promoting synaptic plasticity phenomena [162]. Thus, A1 receptors mostly act as a hurdle in the temporal vicinity of brain insults which need to be surmounted in order for neurodegeneration to begin [162]. In contrast, the blockade of A2 receptors alleviates the long-term burden of brain disorders in different neurodegenerative conditions and also seems to afford benefits in some psychiatric conditions [162].

It is now widely recognized that critical changes in adenosinergic neurotransmission occur within aged brain structures, including the striatum, hippocampus, and cortex [163-168]. An earlier paper by Cunha *et al.* [164] suggested that there are age-related and structurally specific changes in the balance between inhibitory A1- and excitatory A2A-adenosine receptor-mediated actions. Indeed, these authors noticed that in the cortex and hippocampus, the balance might be shifted towards adenosine-mediated excitatory actions, since there is an increase in the number of A2A receptors and a decrease in the number of A1 receptors upon aging. In contrast, in the striatum, the A1/A2A ratio might be only slightly affected in an aged brain. Others reported that in aged animals, the motor inhibitory adenosinergic tone seems to be increased compared to young animals [165]. More recent studies based on the use of positron emission tomography (PET) neuroimaging technique revealed the decreased density of extra-striatal A1 receptors in the cortex and thalamus of patients with Alzheimer's disease [167-169]. Using the same technique, Mishina *et al.* [170] described a decrease in A1 receptors in the human striatum, which correlates with the age-related declines in D1 and D2 receptors, and lack of changes in the distribution of A2 receptors in the function of aging.

4.3. Adenosine/Dopamine Interactions

Adenosine has an essential role in the modulation of dopaminergic activity acting through adenosine receptors - A1 receptors

co-localize with dopamine D1 receptors, and A2A receptors with dopamine D2 receptors in heteromeric complexes [171, 172]. So far, the interaction of adenosine and dopamine receptors has been experimentally confirmed in the striatum [132, 154, 158], globus pallidus [173], limbic structures [174], and substantia nigra pars reticulata [175]. Direct intramembrane A1/D1 and A2A/D2 receptor heteromerization may alter the affinity as well as the G protein coupling and thus the transmembrane signal pathways [171, 172]. Generally speaking, adenosine/dopamine interactions at the behavioral level probably reflect those found at the molecular level of receptor binding and signal transduction [172]. A1 and D1 receptors interact antagonistically, which is vital data for attempts to pharmacologically modulate disorders associated with excessive release of dopamine from intracellular depots. Indeed, negative modulation of post-synaptic dopaminergic transmission, which is a desirable process in case of drug-overuse, can probably be explained by antagonistic interactions between A1/D1 receptors both at the level of binding and the second messengers [129, 136]. The interaction between A1/D1 and A2A/D2 receptors is enhanced in the striatum of the dopamine deficient "weaver" mutation, which serves as a mouse genetic model of Parkinson's disease [176]. All these above discussed studies suggest that adenosinergic system modulates both hyper- and hypoactivity of the dopaminergic system of the brain, and thus motor and non-motor aspects of the organization and realization of behavioral patterns.

4.4. Approaches to Studying Psychostimulant-Induced Behavior

Response to novelty is very complex, and it reflects a desire to explore novelty, novelty-related anxiety, and, regarding the time-dependent profile of the activity, adaptability to the specific environment [177]. Exploration of novel environments enhances brain plasticity and promotes learning [178]. Novelty co-activates the hippocampus [179] and the substantia nigra/ventral tegmental area (SN/VTA) dopaminergic circuits; through a back-projection to the hippocampus dopamine enhances hippocampal synaptic plasticity for novel events and has a motivationally energizing effect, *i.e.*, improves motivation through striatal mechanisms (reward processing and representation in the striatum [180-182]). Thus, although it may sound like easy/incidental, the dynamic of psychomotor response to the novel environment should not be underestimated, especially considering subjects with already existing complex changes in dopaminergic reward circuits due to repeated psychostimulant usage (mentioned in 3.3.). New findings indicate that psychomotor activity observation may serve as a potential objective tool capable of monitoring the course of affective states in everyday life [183].

In neurologically intact rats, which represent the biomedical species of choice for testing drug efficacy, dosage and toxicology for preclinical research having enhanced cognitive abilities and a rich social repertoire paired with neural complexity [184], the locomotor and vertical activities reflect exploratory activity and are also used as an index of psychomotor activation after exposure to low doses of psychostimulant drugs [185]. Rearing or vertical activity is a useful marker of environmental novelty and one of the several ethological measures that can be used to assess information-gathering (and escape) behavior [186]. Stereotypy is typically defined as abnormal, repetitive, and purposeless motor behavior using either frequency-of-occurrence tables, derived from behavioral checklists or interruption of photo beams in a test chamber [187]. The elevated plus maze (EPM) test represents one of the most widely used tests for the study of anxiety-related (approach-avoidance) behavior in rodents and has been recently introduced as the first ecologically valid assay to track actual human approach-avoidance behavior under laboratory conditions [188]. In this test, anxiety is typically measured by indices of open-arm avoidance and general locomotor activity by the frequency of closed-arm entries [189]. In addition to classical parameters measured in the EPM, there are ethological measures (with the accent on stretched-attend postures that reflect approach-avoidance conflict), which permit comprehensive reporting of animal behavior in the maze, thereby proving valuable facts about anxiolytic or anxiogenic action of specific pharmacological treatments. Thus, changes in parameters of motor and approach-avoidance behavior in rodents tested in particular behavioral paradigms could give essential data about the subjective experience of the testing environment, as well as about existing drug-induced changes in the subjective perception of enhancement, threat, and risk. For example, considering that both drug-induced locomotor sensitization and reactivity to novelty in rodents have been related to drug-craving mechanisms in humans, it has been shown that a complex and plastic interaction between the anxiogenic and motivational properties of both novelty and AMPH can modify the behavioral expression of craving-related mechanisms [190].

Psychostimulant-induced behavioral sensitization can lead to supersensitivity and upregulation of D1 receptors in the nucleus accumbens, and substantia nigra pars reticulata after an abstinence period of 24 h to a few weeks [191-193]. Adenosine A1 receptors modulate the release of various neurotransmitters such as dopamine, glutamate, GABA, and acetylcholine [122]. Nevertheless, the release of dopamine and glutamate in the striatum is under the inhibitory control of A1 receptors, and in particular, this endogenous A1 receptor-mediated tonic inhibition can be observed in the ventral striatum (nucleus accumbens) [194, 195]. The blockade of this tonic inhibition leads to increased dopamine and glutamate release, while stimulation decreases the level of these neurotransmitters in the striatum [195]. At first glance, it was suggested that A1 receptor-mediated inhibition of dopamine release in the striatum is secondary, *i.e.*, glutamate-dependent, but it was proven that it is also glutamate-independent [195]. It likely depends on the activation of dopamine D1 receptors [196]. Importantly, it has been shown that the selective activation of central Al adenosine receptors induces anxiolytic-like behavior, while the activation of A2 sites causes locomotor depression and reduces the effects of Al receptor activation [197]. As Al receptors are widely distributed throughout the CNS, including presynaptic terminals where they mediate a potent inhibition of the release of a variety of neurotransmitters (glutamate, acetylcholine, 5-hydroxytryptamine) and some peptides, it has been proposed that an inhibition of release of these endogenous agonists is responsible for Al receptor-mediated anxiolysis, raising the possibility of developing CNS selective purine receptor agonists as novel anxiolytic drugs [197].

Exposure to novelty activates, at least in part, the same neuronal substrate that mediates the rewarding effects of drugs of abuse [198, 199]. Novelty-induced motor activity strongly depends on excitatory glutamatergic inputs to the VTA and consequential elevation of mesolimbic dopaminergic transmission. It has been documented that stimulation of A1 receptor activity in the VTA negatively influenced motor activation [200]. It has also been shown, using an open field test, that novelty-induced locomotor activity is blocked by microinjection of dopamine antagonists directly into the nucleus accumbens [201]. At this point, A1 receptor desensitization as a consequence of repeated or chronic exposure to agonist [202, 203] should not be forgotten. It can significantly affect the outcome of the treatment, *i.e.*, chronic therapy with A1 agents can result in the effects that are opposed to those observed following their acute administration [204-206].

5. RIBAVIRIN: AN ADENOSINE AGONIST WITH STILL ELUSIVE MECHANISM(S) OF ACTION

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide; $C_8H_{12}N_4O_5$) was first discovered and developed in 1970 by chemists Joseph T. Witkowski and Roland K. Robins from the International Chemical and Nuclear Corporation (ICN) [207] and approved for medical use in 1985. It is a synthetic nucleoside analog with a

broad-spectrum antiviral activity against different human and animal viruses including HCV, respiratory syncytial virus (RSV), viral hemorrhagic fever (VHF), influenza, bornavirus, measles, adenovirus, subacute sclerosing panencephalitis (SSPE), human immunodeficiency virus (HIV), *etc*. [3-13]. Ribavirin has also been reported to possess antiparasitic activity by affecting the metabolism of Trypanosoma sp., Plasmodium sp., *etc.* [208, 209]. The beginning of the 21st century marked a shift in interest from the study of antiviral activity of ribavirin to its application in fundamental and clinical neuroscience. These studies are focused on deciphering how ribavirin affects the adaptive functioning of the dysregulated neurons, astrocytes, and microglia. Accordingly, the research related to the CNS virus infections [7], traumatic brain injury [210], experimental autoimmune encephalomyelitis [211, 212] and AMPH-induced locomotor and stereotypic activities [19-21] is one of the most prominent attempts to elucidate the potential therapeutic use of ribavirin in treating CNS disorders. Moreover, some studies suggest that ribavirin may be used as an antitumor drug because of observed dose-dependent and cell line-dependent inhibition of cancer cell growth [213]. So far, the antitumor potential of ribavirin alone or in combination with interferon alfa has been explored through several research and clinical trials, in multiple cancers including acute myeloid leukemia, oropharyngeal squamous cell carcinoma, metastatic breast cancer, glioblastoma, human renal carcinoma, pediatric osteosarcoma, *etc.* [214-218].

5.1. Mechanism(s) of Ribavirin Action

Ribavirin is a prodrug that, after the administration, undergoes successive intracellular phosphorylation to monophosphate, diphosphate, and triphosphate anabolites [219]. The exact mechanism by which ribavirin exerts its antiviral activity is unclear and still under intensive research. In general, it may differ depending on the cell and tissue type, as well as *in vitro* and *in vivo* experimental conditions. Beaucourt and Vignuzzi [11] nicely summarized the current knowledge of molecular and cellular mechanisms of ribavirin antiviral action. Accordingly, (1) the inhibition of inosine monophosphate dehydrogenase (IMPDH) by ribavirin-5'-monophosphate and (2) immunomodulatory effects on antiviral cellular responses (enhancing the T-helper type 1 over type 2 responses or upregulating the interferon-stimulated response element) are two main indirect ways of to combat viral infections by ribavirin. The direct mechanisms include (1) the inhibition of the viral RNA-dependent RNA polymerase (RdRp) through direct interaction with ribavirin-5'-triphosphate; (2) interference with RNA capping activity, and (3) increase of viral mutation rates through the misincorporation of ribavirin into the genome. Identification of a growing number of ribavirin-resistant and sensitive viruses implies the specific mechanisms of its action against different virus infections. Ribavirin is a multi-target drug that greatly contributes to its antiviral effectiveness. In addition to the commonly adopted inhibition of viral replication, it also affects the viral genome. The mutagenic activity of ribavirin may induce erroneous viral replication causing inhibition of virus growth or enhance the selection and survival of mutant viruses that may lead to the inefficacy of ribavirin treatment [220]. Therefore, *via* immunomodulation, depletion of guanozine-5'-trifosfat (GTP) pools, modulation of interferon-stimulated gene expression, interference with viral methyltransferase activity, direct inhibition of the viral polymerase, and inhibition of eukaryotic initiation factor 4E interfering with cap-dependent translation, ribavirin can lead to lethal mutagenesis with potentially favorable as well as unfavorable therapeutic consequences [220-222].

The antiparasitic activity of ribavirin probably involves the inhibition of time-dependent inactivation of the human S-adenosyl-L-homocysteine hydrolase (Hs-SAHH) and *Trypanosoma cruzi* S-adenosyl-L-homocysteine hydrolase (Tc-SAHH), enzymes that catalyze the conversion of S-adenosyl-L-homocysteine to adenosine and homocysteine [208]. Due to structural similarity to adenosine, ribavirin binds to the adenosine-binding site of the two SAHHs and reduces the NAD^+ cofactor to NADH [208].

As a nucleoside analog, ribavirin shows a moderate affinity for adenosine A1 receptors [223]. These receptors are expressed throughout the body, particularly in the brain, and their stimulation through Gi/o proteins leading to inhibition of adenylyl cyclase, reduction of Ca^{2+} entry, and activation of phospholipase C and K^+ channels [122, 149, 150]. Thus, many physiologically- and clinically-relevant effects of ribavirin on different aspects of animal and human physiology, such as nociception, neuroinflammation, and behavior [20, 210, 212, 224], are probably the result of A1 receptors activation in different regions of the brain.

5.2. A Story of Ribavirin Dosage and Route of Administration

Ever since ribavirin was introduced as an antiviral drug, the search for optimal doses, route of administration, combination with other medications, side effects, the emergence of ribavirin resistant variants of viruses, the role of transmembrane transporters and carriers in its uptake, occupies an essential place in clinical pharmacology of ribavirin [8, 11, 225-228]. The dosage and route of administration of this drug are specific for certain types of viruses, the severity of infection, and also depending on the viral genotype [3, 4, 10, 225, 229-231].

Ribavirin is quite often combined and used with other antiviral drugs. For instance, ribavirin monotherapy is not efficacious against chronic HCV, and it usually requires a combination with interferon [10, 225, 232]. The doses of ribavirin and its successful combination with interferon are highly dependent on the HCV genotype. It has been shown that HCV genotype 2- and 3-infected patients require 24 weeks of treatment and a low dose of ribavirin, *i.e.*, 800 mg daily, while HCV genotype 1-, 4-, 5-, and 6-infected patients require 48 weeks of treatment and a higher, body weight-based dose of ribavirin, *i.e.*, 1000-1400 mg daily [232]. In patients who can tolerate ribavirin without significant side effects, cumulative ribavirin exposure and its optimal concentrations are essential for the success of therapy [10]. Therefore, the optimization of ribavirin dose and duration of treatment ensure the highest chance for a durable response to the therapy. In contrast to HCV infection, lower doses of ribavirin, alone or combined with other drugs, are required to treat Chikungunya virus infection. It has been reported that the oral doses of ribavirin (400 mg daily for 7 days) have a direct antiviral effect against Chikungunya arthritis caused by a viral infection [229].

The treatment of HCV based on the combined use of ribavirin and pegylated interferon, such as pegylated interferon alfa-2a and pegylated interferon alfa-2b, which has been validated in large-scale studies and clinical practice, may remain an essential element of therapy [10, 221, 225, 232]. Even more so, triple therapy consisting of DAA plus pegylated interferon/ribavirin is quite effective in treating difficult-to-cure patients infected with HCV genotype 3 or with resistance-associated variants [233]. Three classes DAAs with a significant number of developed drugs such as HCV NS3 protease inhibitor telaprevir or boceprevir are now used solely or combined with ribavirin and pegylated interferon in the treatment of HCV infections [221, 233, 234]. The combinations of different DAAs could be the holy grail of HCV therapy, as some researchers suggest that they have the potential to cure HCV infection completely [221]. Ribavirin and interferon alfa may also exert a strong synergistic antiviral effect against Chikungunya virus infection [235, 236]. *In vitro* studies on Chikungunya virus-infected human cell lines (Vero, HUH-7, and A549 cells) demonstrated cell-line sensitivity to ribavirin, interferon alfa, and favipiravir drugs. While ribavirin was effective in the fight against Chikungunya virus-infected HUH-7 cells, the treatment with interferon alfa and favipiravir has led to substantial reductions in viral burden in clinically achievable concentrations in A549 and Vero lines [237]. Some recent studies reported that antibiotic doxycycline and mefenamic

acid, a non-steroidal anti-inflammatory drug, when combined with ribavirin, alleviate Chikungunya infection symptoms [238, 239].

In animals and humans, ribavirin is given orally, nasally, intravenously, intraventricularly, and intraperitoneally [9, 19-21, 229, 240-242]. Ribavirin, as an aerosol, was the first specific therapy available for RSV infections [240]. Aerosolized ribavirin is very costly, teratogenic, and inconvenient [12]. Instead of using nasal aerosol treatment of RSV, clinicians today are looking toward the promising oral use of ribavirin even in immunocompromised patients. Therefore, it seems that oral ribavirin (600-800 mg twice daily with or without intravenous immunoglobulin) is a well-tolerated treatment for RSV infection in moderately to severely immunocompromised patients [12]. Although some studies did not reach any consensus regarding the effective use of oral *versus* inhaled ribavirin [243], still oral ribavirin appears to be a safe and cost-effective alternative to aerosolized ribavirin for the treatment of RSV infection in immunocompromised patients [244]. Unlike oral and aerosol formulations, the intravenous administration of ribavirin does not have US FDA approval [245]. There are exceptions to these regulations as intravenous ribavirin can, however, be authorized for use as a result of an Emergency Investigational New Drug (EIND) application for patients with acute viral infections, including rare infections for which no alternative treatment is available. So, the oral intake is the main route of administration of ribavirin in case of VHF [246, 247], but there are case reports that the intravenous ribavirin was effective in a few patients with Bolivian hemorrhagic fever [248].

5.3. Side Effects of Ribavirin Therapy

Adequate exposure to ribavirin seems crucial for achieving the best virological response. However, long-term treatment with the combination of interferon and ribavirin aside from systemic side effects, such as anemia and body weight loss [16, 232] is associated with pronounced neuropsychiatric problems including fatigue, mood disorders, anxiety, irritability, emotional ability, and agitation [228, 249, 250]. The exact contribution of each component of combined therapy to the mentioned side effects has not been elucidated, but there is a view that they are mainly related to interferon-alpha [14, 251-255].

Ribavirin mainly shows toxicity at a relatively low concentration (250 to 400 μg/g) [5]. Furthermore, SSPE was treated safely and effectively with a high dose of intravenous ribavirin combined with intraventricular interferon [241], and by intraventricular administration of ribavirin [9]. Tomoda *et al.* [241] reported that high doses and long-term ribavirin treatment improved the neurologic states of patients, but neurologic deterioration was observed a few months after the high-dose intravenous ribavirin therapy was stopped. Because of systemic toxicity, these authors reported that they could not proceed with further intravenous treatment. So as part of their later study or the clinical intervention, Hosoya *et al.* [9] administered ribavirin intraventricularly and observed a less pronounced neurologic and systemic side effects of ribavirin treatment in these patients.

Some of the side effects of ribavirin could be avoided by its structural modification. It has been shown that the *l*-enantiomer of ribavirin (ICN 17261) shows reduced toxicity but antiviral efficacy compared to *d*-nucleoside ribavirin [256]. The other option is ribavirin dose modification or dose adjustment. However, the critical question is how to modify the dose of ribavirin in such a way that the effectiveness of the therapy is not compromised while the side effects are reduced. One way to counter anemia symptoms and to avoid ribavirin dose reduction is to tilt the hormonal balance toward the production of red blood cells. Indeed, some studies have proved that erythropoietin can improve hemoglobin values and maintain ribavirin dosage levels [257, 258]. In addition, the absence of side effects and improvement of patients' quality of life without ribavirin dosage reduction could be achieved by using hematopoietic growth factors such as epoetin alfa and darbepoetin alfa [259].

5.4. Ribavirin and the Brain

In the treatment of brain and non-brain viral infections, a particular challenge is how to distribute ribavirin to the brain effectively, given the difficulties of its transporting through the cell membranes and blood-brain barrier [226]. Indeed, the *in vivo* efficacy of ribavirin towards the cerebral viral load seems to be limited by the selective permeability of the blood-brain barrier [230]. Ribavirin uptake is restricted primarily by concentrative nucleotide transporters (CNTs) and equilibrative nucleotide transporters 1 and 2 (ENT1 and ENT2) in various cell lines [226, 260]. ENT1 protein expression is the highest in structures, such as the adrenal gland, ovary, stomach, small intestine, and colon, while ENT2 protein expression is the highest in neurological tissues, heart muscle, pancreas, *etc.* [261]. A significant difference between these ENTs and CNTs is their sodium dependence [262]. While CNTs are characterized as sodium-dependent with high affinity for nucleosides, thus far, the lower affinity ENTs facilitate bidirectional, sodium-independent transport of nucleosides [261, 262].

Ribavirin, as other antiviral drugs, often shows dramatic difficulties in entering the brain compartments from the bloodstream. The main reason for this long-lasting problem of antiviral pharmacology is that ribavirin and other antiviral drugs are substrates for active efflux transporters (AETs) located in the physiological barriers between blood and the CNS and in macrophage membranes, which actively efflux them into the bloodstream [263]. The attempts to counter this problem are extensively studied. One way is to apply AETs inhibitors, but the co-administration of AETs with antiviral drugs leads to severe side effects [263]. The other way to solve this problem is by using potent drug carriers and innovative technological formulations such as thermoreversible gels, polymeric micro- and nano-particles, solid lipid microparticles, nanoemulsions, absorption enhancers (chitosan, papaverine), and mucoadhesive agents (chitosan, polyvinylpyrrolidone) [263]. For example, Jeulin *et al.* [264] demonstrated that whatever the tested dose (intraperitoneal 40 or 100 mg/kg), the amount of ribavirin in the brain was significantly higher when the drug was injected as a complex with alpha-cyclodextrin, in healthy or measles virus-infected mice.

Despite the difficulties of ribavirin transport through the blood-brain barrier, there is evidence that it still enters the brain. Ribavirin was detected in different brain regions including cerebellum, olfactory bulb, cerebral cortex, basal ganglia, and hippocampus 20 min after intravenous or nasal application at a dose of 10 mg/kg [230], and reached the maximum concentration in the brain at 8 h after a single intramuscular injection of the same dose [265]. The brain bioavailability of ribavirin largely depends on its excretion from the body. It has been shown that 82% of intramuscularly administered ribavirin at a dose of 10 mg/kg was excreted in the urine of rats within 24 h [265], while the total radioactivity in the urine of rats treated intravenously with [^{14}C] ribavirin at a dose of 30 mg/kg encompassed 84% of the initial dose [266].

6. POTENTIAL EFFECTIVENESS OF RIBAVIRIN AS AN A1 AGONIST IN PSYCHOMOTOR-USE DISORDER

Many A1 receptor-mediated effects, observed to a lesser extent or absent under physiological conditions, are markedly increased during pathological conditions, and in that context, they are neuroprotective [20, 118, 267-269]. The specificities in the distribution of A1 receptors and their role in maintaining homeostasis and preventing overactivation in the brain could explain this observation. These receptors are widely expressed pre- and postsynaptically throughout the brain [147, 148], and are involved in the reduction of neurotransmitter release and the modulation of synaptic transmission [122]. The inhibitory effect of adenosine mediated by A1 receptors

is the most prominent on excitatory synaptic transmission (glutamatergic) that is very often completely blocked, while it is less frequent on inhibitory synaptic transmission (GABAergic) [118, 270, 271]. By differentially affecting the excitatory and inhibitory synaptic transmission, adenosine changes the excitation-inhibition balance and causes an overall shift to lower excitability in different brain regions [270, 271]. Also, it has been shown that A1 receptors interact antagonistically with D1 receptors [171, 272-274]. This finding imposes the need for examining the influence of A1 receptors activation on dopamine-mediated processes in the brain and offers a reasonable basis for designing new substances for the treatment of diseases associated with disturbed dopaminergic neurotransmission. Even though targeting adenosine in some pathological states appears attractive and rational, the fact that the same receptors play essential roles in normal or extreme physiology provides a cautionary note [120]. Also, a problem that may arise from the therapeutic use of A1 agonists, especially in the case of chronic dosing, is receptor desensitization, which can progressively reduce the effectiveness of treatment with repeated substance administration [202, 203].

Studies dealing with the effects of ribavirin as an A1 agonist on dopaminergic neurotransmission in the brain are scarce. So, it has been shown that ribavirin applied intraperitoneally (i.p.) at doses of 10, 20 or 30 mg/kg did not significantly affect either basal locomotor or stereotypic activities, while pretreatment with doses of 20 and 30 mg/kg significantly decreased only AMPH (1.5 mg/kg, i.p.) - induced hyperlocomotor response [20]. The obtained results revealed the ability of ribavirin to pass the blood-brain barrier, enter the brain, and modify synaptic transmission, especially in conditions when it is disrupted. The existence of regional differences in sensitivity to ribavirin was attributed to its unequal distribution, heterogeneous expression of A1 receptors, and/or differences in the intensity of A1-D1 receptor-receptor interaction in subregions of the basal ganglia. In our recent work (in drug-naive rats), it has been shown that 7-day ribavirin treatment (10 and 30 mg/kg/day, i.p.), in addition to a decrease in novelty-induced motor activity, also produced a significant reduction in body weight gain in treated animals compared to controls [21]. We explained these findings by the ability of 7-day ribavirin treatment to provoke peculiar changes in the regulation of midbrain dopaminergic system activity, thus influencing/diminishing physiological (novelty-induced motor activity and food-directed behavior) responses that depend on it. Briefly, the regulated release of dopamine is essential for sustained feeding [275], and consumption of food is related to dopamine transmission in several regions of the striatum (in the caudate putamen for response to the caloric value of food and regular feeding, in the nucleus accumbens for the rewarding aspect of feeding) [276]. The A1 receptors, which antagonistically modulate the activity of dopamine D1 receptors [171, 272-274], are highly abundant in the mesolimbic system of the brain, especially in the ventral striatum and nucleus accumbens [277] and their overactivity produces hypophagia [278]. Given the affinity of ribavirin for A1 receptors [223], the physiological/neurobiological consequences of prolonged ribavirin administration could largely depend on previous drug exposure.

In the material discussed above, we considered some aspects of ribavirin action and its potential application in conditions of disturbed dopaminergic neurotransmission, but still there are many questions about the benefits and side effects of its treatment. One of the challenging domains is the detection of ribavirin in the brain tissue. Although several methods have been described for ribavirin determination in plasma [279, 280], its detection in the brain seems to be more complicated. Free ribavirin concentration in mice brain was measured by Jeulin *et al.* [264], but recently a specific method for ribavirin determination in brain tissues by liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been developed and deemed satisfactory in terms of selectivity, sensitivity, and accuracy [281]. Overall, these findings indicate that the combined work of scientists from different disciplines is essential to fully define the correlation between physiological consequences of ribavirin usage and actual drug concentration at the time of testing. Implementation of the model by age, gender, and the baseline features of metabolic activities of the examined model systems should be considered as well.

CONCLUSION AND FUTURE PERSPECTIVES

This multifaceted review tried to accentuate complex neurochemical/neurobiological changes that may appear in the drug-addicted brain *per se* and after the usage of ribavirin, a nucleoside analog with a moderate affinity for adenosine A1 receptors. Ribavirin has been used as an antiviral agent for several decades, continuing to be a critical antiviral agent in treating HCV for which substance abusers are at higher risk. Numerous patients who start antiviral therapy for HCV do not perform it through the entire course of treatment because of the side effects that are not insignificant. Moreover, these side effects are still mostly unexplored on account of already existing changes in the brain due to previous drug usage. Specific neurobehavioral states related to psychostimulant misuse in patients with HCV infection may complicate acceptance and reaction to the antiviral treatment. This issue is, overall, highly delicate. It should be mentioned that throughout contemporary history, it has been suggested that antiviral therapy for HCV should not be conducted in those with recent and current drug usage, although people who inject drugs represent a key HCV-affected population, which was excellently summarized by Grebely *et al.* [282] who strongly recommended that there is no good ethical or health-based evidence for such discriminations.

The conceptualization of addiction as a brain disease reflects in part findings from brain imaging studies and preclinical research that have identified the brain circuits that are disrupted by the drugs. It should be noted that the treatment of psychostimulant addiction remains a significant problem worldwide and a big challenge because there are no corresponding forms of pharmacological interventions that have met the criteria for regulatory approval or generally accepted use [283]. Recovery in psychostimulant drug-dependent individuals is particularly challenging because psychostimulant drugs induce significant changes in the brain regions associated with learning/memory, decision making, impulsivity, motivation, and impaired control of behavioral output [284]. As it has already been accentuated [27], integrated care is fundamental for the treatment of infectious (communicable) diseases, such as HCV and parallel treatment of the substance use disorder as well.

Facts presented in this manuscript suggest that different psychomotor and neurobehavioral reactions to ribavirin could be expected in drug-naive and psychostimulant drug-dependent individuals, but this presumption needs additional examination and experimental confirmation with respect to a particular drug, as there are fundamental differences in mechanisms of action among psychomotor stimulant drugs (*i.e.*, [285]) and the important role of dose in determining psychostimulant action [75]. We have tried to accentuate this important topic in our recent research article devoted to psychomotor and physiological response to low ribavirin doses in a rodent model, emphasizing the role of the treatment duration [21, 232]. Our previous research also indicates that low doses of ribavirin can modulate behavioral response induced by AMPH [19-21] implying its possible application in counteracting psychostimulant-induced effects. The view that the potential adenosine A1 receptor agonists could be used as an effective strategy to counteract psychostimulant-induced effects has also been posted by others [128]. Once again, although ribavirin has not been primarily assessed as a neuroactive drug, and we do not know its specific mechanism(s) of action, the behavioral changes in particular experimental settings confirm that this drug affects the brain. Thus, more effective promotion of mental health problems related to the

central effects of antiviral drugs/ribavirin usage is needed among neurobiologists to encourage the basic studies that will work on this question of clinical relevance.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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