Methamphetamine and Sleep: Neurobehavioral Correlates and Molecular Mechanisms

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Abstract

Methamphetamine is a potent and highly addictive psychostimulant, and one of the most widely used illicit drugs. Over recent years, its global usage and seizure have been on a rapid rise, with growing detrimental effects on mental and physical health, and devastating psychosocial impact pressing for intervention. Among the unwanted effects of methamphetamine, acute and long-term sleep impairments are of major concern, posing a significant therapeutic challenge, and a cause of addiction relapse. Unraveling mechanisms and functional correlates of methamphetamine-related sleep and circadian disruption are, therefore, of key relevance to translational and clinical psychiatry. In this article, we review the evidence for the acute and long-term deficit of sleep-wake behavior and circadian activity caused by single or recurring methamphetamine usage and withdrawal. Factors contributing to the severity of sleep loss and related cognitive deficit, with risks of relapse are discussed. Key molecular players mediating methamphetamine-induced dopamine release and neuromodulation are considered, with wake-promoting effects in mesolimbic circuits. The effects on various sleep phases and related changes in dopamine levels in selected subcortical structures are reviewed and compared to other psychostimulants with similar action mechanisms. A critical appraisal is presented of the therapeutic use of modafinil, countering sleep and circadian rhythm impairments. Finally, emerging knowledge gaps and methodical limitations are highlighted along with the areas for future research and therapeutic translation.

Keywords: methamphetamine; sleep and insomnia; dopamine; addiction; modafinil; drug abuse; circadian rhythms; dopamine transporter

Introduction

Amphetamine-type psychostimulants such as amphetamine and methamphetamine are amongst the most widely used and abused illicit drugs, with the annual prevalence estimated between ~15.2 and ~42.9 million users worldwide in 2017 [1,2]. As a major contributor to the global drug problem and related health issues, methamphetamine dominates the illegal market, with over 2009-2017 the number of seizures quintupled [1]. Fig. 1 summarizes the proportion of the harm caused by the use of amphetamines amongst the major abused drugs in 2017 with their chemical structures and relations (Fig. 1A-B). The increased availability and growing use of amphetamine-type stimulants, and methamphetamine in particular, with grave consequences for consumers and society, impose an increasing pressure on medical services and healthcare in general [3]. Long-term abuse of methamphetamine for performance enhancement, self-medication to cope with stress, as well as a substitute to opioids has been associated with detrimental acute and long-term psychosocial and health consequences (for reviews see [2,4-8]). As a potent psychoactive drug, methamphetamine enhances the level and activity of three major monoamines - dopamine, serotonin, and norepinephrine in reward brain circuits, with the majority of studies focusing on its effects on dopaminergic drive [9]. The increase of dopamine activity by methamphetamine is largely due to selective inhibition of two molecular targets located at dopaminergic synaptic terminals, the vesicular monoamine transporter-2 (VMAT-2), and dopamine transporter (DAT), stimulating a strong reward response and reinforcement processes. The details of the action mechanisms of methamphetamine have been described and discussed in several excellent reviews [2,10-13].

The most wanted effects of methamphetamine on cognitive and emotional spheres include euphoria, enhanced energy and alertness, feeling of increased mental and physical capacity, accompanied by a surge of performance and productivity [14,15]. The spectrum, timing, and intensity of these effects depend on the dose, form of the used drug (crystalized,

powder, and pills) and route of administration [16]. These effects of methamphetamine are typically accompanied by transient or long-term disruptions of several major physiological and homeostatic processes, which manifest in hypertension, hyperthermia, tachycardia, attentional and cognitive impairments, and impairments of sleep, with the latter being one of the most undesirable outcomes of methamphetamine use and withdrawal [17]. Chronic methamphetamine users generally take the drug repeatedly over a few hours or days, which causes lasting sleep disturbances [2,18]. During escalating drug intake, the sought after effects of methamphetamine become less pleasurable, whereas the unwanted consequences grow more prominent [16]. Methamphetamine withdrawal, on the other hand, can cause hypersomnia and impairments of the sleep-wake behavior and circadian rhythms, amongst other adverse effects [19,20]. It is thought that abstinence-related sleep disturbances in methamphetamine users play a significant role in the regression of addicts to the abusive state, as compared to individuals with relatively intact sleep characteristics [21].

There is overwhelming evidence suggesting that disruptive effects of methamphetamine on sleep result from changes in the dopaminergic drive, which is known to play an important role in regulating the sleep-wake cycle and the circadian activity [22-25]. Sleep-wake cycle regulation by dopaminergic circuits has two principal components: (1) the wake-promoting circuits of the ventral tegmental area (VTA) and dorsal raphe nucleus (DRN) innervating the ventral striatum and prefrontal neurons [23,26,27], and (2) the sleep-promoting circuits of substantia nigra (SN) innervating dorsal striatum [28,29]. The effects on the dopaminergic drive on circadian activity, on the other hand, depends on (1) modulation of the circadian pacemaker in the suprachiasmatic nucleus (SCN), and (2) suppression of melatonin release from pineal gland [25,29,30]. The later entails circadian rhythm-dependent alterations in D_4 receptor expression and inhibition of adrenergic inputs to pineal neurosecretory cells [30].

The current understanding of methamphetamine effects on sleep and circadian rhythms is largely based on reports in rodents and primates, as well as clinical studies in humans. Despite major research advances, there is an unmet need in mechanistic and translational research, given the therapeutic relevance of the topic. Moreover, considerable differences in experimental design and choice of models in sleep and circadian rhythm studies with conflicting reports hinder the data compatibility and interpretation, warranting further research with critical analysis. In this article, we review preclinical and clinical studies of the effects of methamphetamine use and withdrawal on sleep-wake behavior and circadian rhythm in primates and humans. We consider cellular and molecular mechanisms underlying the disruptive effects of methamphetamine and discuss major advances as well as outstanding challenges. Finally, we consider the relevance of emerging data to translational neurobiology and clinical psychiatry and present outlook for future developments.

Clinical studies of methamphetamine effects on sleep in humans

The major symptoms induced by methamphetamine use in humans can be divided into the following 3 categories: (1) positive psychotic symptoms such as suspiciousness, unusual thought content, hallucinations, and bizarre behavior; (2) affective symptoms including depression, suicidality, guilt, hostility, somatic concern, and self-neglect; and (3) psychomotor symptoms such as motor hyperactivity, tension, excitement and distractability [31]. In humans, as part of hyperactivity symptoms, methamphetamine use and withdrawal have been shown to have disruptive effects on sleep duration and quality. Indeed, methamphetamine extends the latency of sleep onset, and markedly decreases the total sleep time [2,17]. Acute methamphetamine withdrawal (measured by Amphetamine Withdrawal Questionnaire; AWQ) [32], also extends the latency of sleep, increases the total nighttime and daytime sleep with extended awakening periods and deteriorates sleep quality, measured by

self-report St Mary´s Hospital Sleep Questionnaire (SMHSQ) [33,34]. To evaluate the relationship between self- reported sleep habits and drug use variables, participants who met DSM-IV-TR criteria for a methamphetamine use disorder (MUD) were assessed with self-report questionnaires, including the Pittsburgh Sleep Quality Index (PSQI) [35] and the Epworth Sleepiness Scale (ESS) [36,37]. Individuals diagnosed with disorders due to methamphetamine use were found to have poorer sleep quality when compared with drug-free controls [35]. In the same study, no significant correlations were found between demographic traits such as age and education and drug use characteristics (duration of abuse, the amount used per day, number of users in the prior 30 days) on both PSQI and ESS scores. Methamphetamine users, who were poor sleepers, as defined by the PSQI, also revealed higher daytime sleepiness when compared to good sleepers [37]. It should be noted that in this study there is insufficient clarity in participants' diagnosis, as DSM-IV-TR criteria differentiate two methamphetamine-related mental health disorders: substance dependence and substance abuse, and it is not clear which of these two the participants met. In a subsequent study, Tang and co-workers examined sleep characteristics in a large group of methamphetamine users (n = 962) who met the DSM-IV-TR criteria for substance dependence, comparing subjective data, using the PSQI [38]. Accordingly, ~54.16% of participants reported poor sleep quality, while ~32.64% suffered from severe sleep problems [38].

It is noteworthy that comparative analysis of the effects of a single intranasal dose of methamphetamine on objective and subjective sleep measures [17] has shown inconsistent results. This may underscore the intrinsic limitations of sleep behavior studies relying exclusively on self-report, and urges for cautions interpretation of emerging data [34,37,38]. Indeed, the study by Perez and colleagues demonstrated that self-reported data may overestimate the extent of sleep disruptions produced by methamphetamine when compared

to objective measures [17]. It should be also noted that this report is based on a relatively small experimental group and needs independent verification. In the same vein, subjective measures of sleep over 4 weeks of methamphetamine withdrawal, using the Sleep Inventory Questionnaire [39], have shown that during the first week, subjects felt significantly more refreshed after awakening in the morning, however, their sleep quality worsened during the second week of withdrawal [40]. Similar to the previous report, Mancino et al. study [40] was based on relatively small sample size and lacked controls for the abstinence condition. It is important to note that, both subjective and objective neurophysiological measures (e.g. total sleep, total non-REM sleep, and sleep efficiency) have shown that on the first day of drug intake, in a small group of participants, methamphetamine (10 mg, oral) caused sleep disruptions relative to baseline controls, whereas such disruptions were not found after repeated use of the drug [41]. The latter suggests that tolerance can develop to the adverse effects of methamphetamine on sleep. These findings are in agreement with the results from another study [42] which showed that combined use of alcohol and methamphetamine attenuate methamphetamine-related sleep disruptions. A follow-up report from the same group elucidated the effect of methamphetamine use on memory formation, using emotionally positive, negative, and neutral pictures, applying objective (actual hours slept, sleep latency), and subjective (estimated hours slept, falling asleep easily) metrics [43]. It was found that after receiving 20 mg of methamphetamine, half of the participants exhibited sleep disturbances (i.e. less than 6 hours of sleep), while the second half failed to show any changes in sleep duration (i.e. slept for more than 6 hours). Notably, the quality of sleep has been found to play a critical role in memory function [44,45]. Methamphetamine administered before viewing pictures (encoding phase) induced memory enhancement in adequate sleepers but caused memory impairments in poor sleepers [46]. A recent double-blind, placebo-controlled polysomnography examination of the effects of recreational use of methamphetamine on

early hours of sleep showed a dose-dependently increased sleep latency and decreased total sleep time, sleep efficiency, REM periods, and total REM sleep duration [47]. **Tables 1 and 2** summarizes the results of acute and long-term methamphetamine effects on sleep parameters.

Overall, the data from clinical studies and the results of the meta-analysis are consistent with the wake-promoting effects of methamphetamine and suggest drug-induced sleep impairments as one of the most prevalent and undesired outcomes [48]. Interestingly, while a single time drug use has acute effects on sleep, its repeated use leads to the development of tolerance with recovery of sleep quality. Sleep impairments during methamphetamine withdrawal, on the other hand, are accompanied by the increased risk of relapse with enhanced craving. Nevertheless, the results of clinical trials require cautious interpretation, with a careful review of the study design, including the psychosocial background of subjects, as well as parameters selected for analysis. Indeed, a widely varying dose range, delivery routes, number and time of drug administration, as well as relatively small sample size call for larger and better controlled trials.

Preclinical studies of methamphetamine effects on sleep in nonhuman primates

Nonhuman primates provide a superb translational model for investigating neurophysiological and behavioral consequences of drug abuse, owing to phylogenic proximity of their neurochemistry and pharmacodynamics to humans. Methamphetamine self-administration has been widely used for experimental research in rhesus monkeys [49-51], applied together with actigraphy for monitoring general psycho-motor activity [52]. Analysis and comparison of various sleep parameters (efficacy, latency, and fragmentation) in rhesus monkeys showed that self-administration of methamphetamine (0.03 mg/kg) leads to disruption of the sleep-wake cycle, an effect which has not been observed at lower doses (0.01 mg/kg) [50]. Importantly, data from the same group show that after discontinuation of

methamphetamine use, all major sleep parameters rapidly returned to the control levels [50]. A dose-dependent increase in nighttime activity with prolongation of the latency of sleep onset and shortening of its duration (measured by actiwatch) were reported also in rhesus monkeys after the intramuscular administration of amphetamine (0.1, 0.3 or 1.0 mg/kg), as compared to saline-injected group [53]. Repeated methamphetamine self-administration in rhesus monkeys over five consecutive days led to development of tolerance to sleep-disrupting effects of the drug, while short breaks between drug intake sessions obviate the development of tolerance [51], in agreement with similar findings of human studies [41,42].

Another area of analysis of methamphetamine effects in rhesus monkeys has been the assessment of changes in sleep patterns during cue- and drug-induced reinstatement of drug-seeking behavior. In a study by Berro and colleagues [54], adult monkeys self-administered 0.01 mg/kg methamphetamine once a day over 7 days, with the availability of the drug signaled by white light (discriminative stimulus). After completion of fixed-ratio 20 schedules, the white light was changed to red (cue-inducement), which was followed by methamphetamine infusion. The extinction sessions after completion of fixed-ratio 20 were not followed by red light and animals received a saline infusion. In the absence of drug and drug-paired cues, the nighttime activity of rhesus monkeys decreased, as compared to rhesus monkeys with unremitting methamphetamine self-administration [54]. However, priming injection of 0.1 mg/kg, but not 0.03 or 0.3 mg/kg, followed by red light (cue-inducement), caused reinstatement, with a reduction of sleep-like behavior the following night [54]. Based on these observations it was tentatively concluded that acuminating drug-seeking behavior during the presentation of drug-paired stimuli impairs sleep. Unfortunately, the authors did not test separately drug- and cue-induced reinstatement effect on nighttime activity.

At this stage, it is important to note that similar to human studies, research of the effects of methamphetamine on sleep behavior in nonhuman primates is at the preliminary

stage. Although highly instructive, longitudinal monitoring of sleep-related motor activity changes in monkeys presents an indirect measure of sleep behavior. Henceforth, the results of actigraphy-based sleep experiments should be treated with a degree of caution, and warrant independent verification with the use of more direct tests. Indeed, actigraphy cannot substitute sleep polysomnography, as it does not provide readouts of cortical activity, with experimental readouts liable to various biases and errors [55]. Nevertheless, data from self-administration studies in primates are consistent with findings reported in humans, demonstrating significant sleep impairments induced by a single time methamphetamine use. Repeated administration of methamphetamine in monkeys, like in humans, leads to the development of sleep tolerance. The results of experiments testing the effects of methamphetamine use and withdrawal on various sleep parameters of nonhuman primates are summarized in Table 1 and 2.

Sleep impairments as a risk factor for methamphetamine use and addiction

In addition to emerging evidence for transient and lasting impairments of sleep and circadian activity by methamphetamine, considerable data suggest a reverse association between sleep disruptions and methamphetamine use and addiction [56,57]. Circadian rhythm abnormalities are viewed as one of the key factors prompting and reinforcing the use of psychostimulants. The most common causes of circadian disruption in humans are jet-lag and night-shift work. Accordingly, substantial clinical evidence suggests that jet-lag is strongly linked with increased consumption of alcohol in international travelers [58], while night-shift working nurses showing higher rates of smoking as well as the use of alcohol and psychostimulants [59]. In experimental rats, it was reported that a two weeks jet-lag experience during abstinence period following two weeks of methamphetamine administration notably increased the propensity of the animals to resume methamphetamine consumption when the drug became

available after a period of abstinence [60]. A human study, on the other hand, has demonstrated that a single dose of methamphetamine (5 mg or 10 mg) attenuates disruptive effects of night-shift work on mood and cognition [61,62]. The authors speculate that the wake-promoting benefits of methamphetamine render the night-shift workers more susceptible to its abuse and addiction, a notion supported also by the results of a study in rats [60]. Kirkpatrick and colleagues showed that methamphetamine is more likely to be taken before the work when individuals are partially sleep-deprived, although its self-administration did not vary as a function of shift condition [63].

At cellular and molecular levels, the use of methamphetamine [13], similar to REM sleep deprivation, enhances dopamine receptor sensitivity [64], with rats after 96 h REM sleep deprivation showing greater psychomotor response to dopamine agonist apomorphine [64]. Accordingly, the results of the autoradiographic analysis demonstrated that 96 h REM sleep deprivation increases the binding of the D_2 subtype dopamine receptor antagonist [^{3}H]-spiperone [65]. Moreover, high-performance liquid chromatography measurement of dopamine metabolites has shown a significant increase in dopamine catabolism in the rat brain during REM sleep rebound, which was preceded by 96 h REM sleep deprivation [66]. It must be stressed that all sleep-related data acquired in rats should be interpreted with a degree of caution, given that the laboratory rats display primarily nocturnal activity pattern and have inherently fragmented sleep, in contrast to monophasic or diphasic sleep in adult humans and nonhuman primates [67]. Taken as a whole and despite differences in models and experimental approaches applied, it emerges that sleep disruptions not only result from methamphetamine use but might reinforce its abuse and facilitate the relapse. The later should be closely considered in order to facilitate the development of effective management and therapeutic approaches.

Reversing methamphetamine-induced sleep impairments by modafinil

High incidents of relapses with the emerging role of sleep impairments by methamphetamine prompted considerable interest in developing therapies restoring the sleep. Currently, there are limited pharmacological options for the treatment of MUD, including sleep impairments related to the use of methamphetamine [2]. Table 3 presents a summary of all registered ClinicalTrials.gov interventions containing the term methamphetamine. From five medications included in multiple randomized trials, four i.e. methylphenidate, bupropion, modafinil, and naltrexone showing limited evidence for reducing methamphetamine use [68,69]. Amongst these, modafinil is considered as a promising candidate for the management of excessive sleepiness related to methamphetamine withdrawal [70]. Mahoney and colleagues demonstrated that a single dose of modafinil (200 mg) reduced daytime somnolence after short-term methamphetamine abstinence [71]. The same group also reported that modafinil reduced subjective ratings of sleep impairments, and suppressed the urge of taking a nap. Importantly, there is a strong positive correlation between the likelihood of taking a nap and craving, as well as the odds of drug use. An earlier clinical study in humans administrated with modafinil (400 mg) over 10 days of methamphetamine withdrawal revealed remarkable improvements in sleep parameters. Positive effects were also found in the context of the withdrawal syndrome, which was milder in modafinil administered group, as compared with a group treated with mirtazapine, a fast-acting antidepressant with dual noradrenergic and serotonergic effects [72]. Using PSQI and ESS tests in 80 patients in double-blind randomized controlled two months study with 200 mg/kg modafinil, it was demonstrated that modafinil improves the sleep quality in patients with methamphetamine withdrawal [20]. On the contrary, another report found no difference in withdrawal severity, craving, and sleep restoration between groups treated with modafinil during methamphetamine withdrawal (200 mg first 5 days and 100 mg on days 6 and 7) as compared to a group treated with placebo [73].

Although there is a consensus that modafinil promotes a wakeful state via an increase in extracellular dopamine in mesolimbic structures, this view needs rigorous experimental confirmation. In experimental rats, such effect has been verified by measurements of the extracellular dopamine level, using microdialysis *in vivo* as well as *in vitro*, an effect attributed to inhibition of dopamine transporter activity [74]. In agreement with such mechanism of action, the results of positron emission tomography (PET) in both nonhuman primates [75] and human subjects [76] suggest blockade of dopamine transporters and increased dopamine activity by modafinil. In non-human primate studies, for instance, it was shown that modafinil exhibits a pharmacological profile characteristic to psycho-motor stimulants such as cocaine [75]. These results are in agreement with observations made previously [74,76,77], demonstrating that modafinil binds and inhibits the dopamine transporter and increases the extracellular dopamine level, which is linked to enhanced nighttime locomotor activity [75]. It is worth stressing that although modafinil and amphetamines might share common pharmacological targets, there seem to be important differences in their action mechanism [78]. For example, in a rat study using EEG recordings, it was shown that modafinil analog armodafinil (R-enantiomer of modafinil) and methamphetamine have a similar wake-state promoting effect [79]. However, unlike methamphetamine, causing rebound hypersomnolence upon its acute withdrawal, armodafinil did not induce such effect [79]. These findings agree with the results of earlier report showing no rebound hypersomnolence in rats after modafinil treatment [80]. Review of preclinical and clinical studies of modafinil abuse liability led Myrick and colleagues to conclude that it has a limited addictive potential [81], with very rare clinical case reports of modafinil dependence, where the drug was utilized for the treatment of conditions unrelated to methamphetamine use [82,83]. It has been also long recognized that repeated administration of addictive drugs sensitizes the mesocorticolimbic dopaminergic system [84] which is manifested via enhanced psychomotor response to dopaminergic receptor

agonists [85]. Under such settings, sensitization of the dopaminergic system is viewed as a key for the addiction [84,86]. Although the administration of modafinil in mouse was shown to cause behavioral sensitization [87-89], such action appears to be species-specific, as these results could not be replicated in rat studies [90,91].

To summarize, from the above-reviewed studies, it emerges that modafinil has a unique potential as replacement therapy for better management of methamphetamine-induced sleep difficulties, to reduce craving and assist in the withdrawal. Nonetheless, results of these reports need independent verification in several preclinical models and randomized human trials, to facilitate clinical translation of modafinil and its analogs for therapeutic interventions.

Neurobiological correlates of sleep impairments induced by methamphetamine

The neurobiological mechanisms of monoaminergic regulation of sleep-wake behavior have been investigated in considerable detail [26,92,93]. Stimulation of dopamine secretion by methamphetamine is thought to be mediated largely via inhibition of the vesicular monoamine transporter-2 (VMAT-2) and the dopamine transporter (DT) at dopaminergic terminals (Fig. 2A, B). An increase in extracellular dopamine activity stimulates a reward response in the mesolimbic system, promting the insomniac state [2,9]. Over decades, little changes in the discharge rate of midbrain dopaminergic neurons during the sleep-wake cycle other than bursting during paradoxical sleep have been viewed as evidence of these neurons not related to sleep. Transgenic modifications that enhance dopaminergic transmission, such as deletion of the DT gene, causing increased wakefulness [94], whereas deletion of D2 receptor decreasing wakefulness [95], however, challenge this view and support the importance of midbrain dopaminergic neurons in controlling the sleep-wake behavior. Recent optogenetic studies demonstrated that activation of DA neurons in VTA but not in SN increases

wakefulness [29,96]. These effects are mediated by VTA projections to the nucleus accumbens (NA), because optogenetic activation of DA terminals in NA, but not in other regions, also promoted wakefulness. This specific DA circuit is, therefore, viewed as a node that regulates the wake-promoting effects of methamphetamine. It must be noted that the dopamine-dependent activation of the waking state is not specific to amphetamines, but can be promoted also by other inhibitors of DT, including bupropion, methylphenidate, and cocaine [9,92]. Interestingly, induced by methamphetamine changes in sleep might result also from inhibition of small-conductance Ca^{2+} activated K^{+} currents in midbrain dopaminergic neurons [97], enhancing their firing activity and dopamine release (Fig. 3A, B). Finally, a genetic mouse model with depletion of cerebral microglia [98] casued attenuation of wake-promoting effects of methamphetamine [99], which emerges to be partly due to the activation of nitric oxide synthases (NOS) [99], known as a potent sleep regulator [100,101]. Of note, methamphetamine can also stimulate the release of cytokine interleukin-1β (IL-1β) from microglia [99]. Like NOS, IL-1β is a potent sleep regulator, acting via interleukin 1 receptor [102]. Research in IL-1β mouse models showed that activation of interleukin 1 receptor and downstream signaling must be intact to warrant methamphetamine and sleep deprivation-induced hypersomnolence [103].

The role of other monoamines in methamphetamine-induced modulation of the sleep-wake cycle has been also investigated. Microdialysis in rhesus monkeys showed that amphetamine causes a surge of dopamine activity at the dose necessary for promoting a wakeful state, an effect abolished by a 5-HT_{2A} receptor antagonist M100907 [53]. This finding agrees with the results of the earlier study showing that antagonizing 5-HT_{2A} receptor attenuates both, amphetamine-induced increases in dopaminergic drive [104] and psychostimulant effects of cocaine [105]. Howell and colleagues used a self-administrated paradigm in primates to show that M100907 and 5-HT_{2C} receptor agonist WAY163909 attenuated the disruptive effects of methamphetamine on sleep [106]. Actigraphy readouts show

that activation of 5-HT_{2C} and inhibition of 5-HT_{2A} receptors improve sleep efficiency, decrease sleep latency, and mitigate the disruptive effects of methamphetamine [106]. Of note, the restorative effects of 5-HT modulators on sleep did not reduce the intake of methamphetamine on the following day [106]. On the other hand, $GABA_A$ receptor enhancers temazepam and eszopiclone were ineffective in preventing methamphetamine-induced sleep impairments, even though they antagonized methamphetamine-induced activation of dopamine release in NA [51]. It was concluded that although dopaminergic drive plays a key role in the wake-promoting effects of methamphetamine, modifications in dopamine activity alone cannot fully account for sleep impairments caused by this psychostimulant [51].

Changes in dopaminergic drive induced by methamphetamine have been confirmed also in humans. In long-term methamphetamine, amphetamine and cocaine users alike, striatal dopamine release as well as DT and D_2/D_3 receptor availability are strongly reduced, as compared to drug-free controls [107] (Fig. 3 C). These changes agree with a well-known decrease in D_2/D_3 receptor availability in the striatum of subjects with acute sleep deprivation, as revealed with the use of D_2/D_3 receptor radioligand [^{11}C] raclopride [76,108,109]. Interestingly, Volkow and colleagues [109] used methylphenidate, another potent blocker of the dopamine transporter, and found no change in striatal D_2/D_3 availability between groups with and without sleep deprivation. In the same study but in rats, an increase in dopamine activity induced by methylphenidate did not differ between the sleep-deprived and the control groups [109]. The authors suggest that reduced D_2/D_3 availability reflects expressional downregulation rather than increased dopamine levels in specific brain areas [109]. It is worth noting that reduced striatal D_2/D_3 receptor availability is not drug-specific, as it is observed also in abusers of alcohol [110] and heroin [111]. These findings have been replicated in methamphetamine addicts, using another high-affinity D_2/D_3 receptor radioligand, [^{18}F] fallypride [112]. Although the relationship between the sleep impairments in drug abusers and

the availability of striatal D_2/D_3 receptors remains to be determined, the downregulation of the D_2/D_3 receptor might contribute to psycho-motor symptoms caused by methamphetamine [113]. Because D_2/D_3 receptor availability in methamphetamine users is thought to be a risk factor for relapse in drug abusive state, careful consideration of these processes with pharmacological and genetic adjustments might improve the outcome of future therapeutic interventions [109]. In this context, the function of the D_4 receptor has generated much interest, owing to its alleged role in regulating circadian rhythms [29,30], as well as the association of the *DRD4* gene with methamphetamine abuse [2,9,114]. Recent studies of genetically modified *drd4* mice with pharmacological manipulations of D_4 activity have confirmed its importance in methamphetamine addiction with circadian impairments [115]. Consistent with these findings, a human study [116] showed that hypermethylation of *DRD4* is linked with a higher risk of methamphetamine addiction.

Concluding remarks

As a potent psychostimulant, methamphetamine is used predominantly as a recreational and performance-enhancing drug. It is also utilized for managing stressful life events, and to a lesser extent for body weight control, and to obtain a synergistic high or to balance the sought after effects of opioids [117-119]. The boost of energy and alertness, euphoria, increased sexuality, and other effects of methamphetamine come with the transition of users from a state of casual to compulsive use, with increasing demand for a higher dose. As discussed, impairments of sleep and circadian activity emerge to play a key role in development of methamphetamine addiction, and particularly in relapsing the addictive state, despite the development of tolerance to sleep-altering effects of methamphetamine. While major advance has been made in elucidating the effects of methamphetamine on sleep, both, preclinical and clinical studies leave open numerous questions and are compromised by methodological

weaknesses. Also, long-term methamphetamine users frequently have comorbidities such as attentional deficit disorders (ADHD), depression, human immunodeficiency (HIV), hepatitis C [16], and slowly progressing neurodegenerative process, known to cause sleep disturbances on their own, which have to be distinguished from the effects of the drug [120,121]. These and other open questions render the interpretation of methamphetamine-induced sleep disruption data challenging. Nevertheless, a view that emerges clearly from preclinical and clinical studies is that while on one hand, stimulants such as amphetamines are attractive for people with disturbed sleep-wake cycles and poor sleep quality, their use deteriorates the sleep quality and impairs circadian activity. This sets a vicious circle, which promotes self-perpetuating methamphetamine use and relapse, with detrimental effects on mental health. Elucidating molecular and circuit mechanisms of sleep impairments, hence, not only should facilitate the development of effective interventions restoring sleep and circadian activity but pave a way towards the treatment of other disorders related to methamphetamine use.

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Figure legends

Figure 1. Illicit drugs and drug use-related harm. (A) A summary histogram presenting a comparison of the harm caused by the use of alcohol and illicit drugs to users and others in 2017. Data are presented as a percentage of the total number of users (100%). Note that methamphetamine and amphetamine hold a leading position in the list (in blue). Modified from Drug harms in the UK: a multicriteria decision analysis by D. Nutt, L. King, and L. Phillips, on behalf of the Independent Scientific Committee on Drugs. The Lancet. Reproduced from [122]. (B) Methamphetamine and its primary metabolites, with some used as illicit drugs.

Figure 2. Neurobiological mechanisms underlying methamphetamine effects in the brain. (A) Illustration of the changes in normal presynaptic terminal included by methamphetamine (top and bottom, respectively). SV – synaptic vesicles; Meth – methamphetamine; DA – dopamine; VMT – vesicular monoamine transporter; DAT – dopamine transporter; DAR – dopaminergic receptors. Note an increase in the level of extra-vesicular dopamine and reduction of its amount within synaptic vesicles. Modified with permission from Kish 2008 [123]. (B) Effects of Nicotine, Ethanol, Cocaine, and Methamphetamine on the output of dopamine from the nucleus accumbens collected with microdialysis. Results are expressed as mean ± SEM of values obtained from 4-5 rats. Modified with permission from Di Chiara and Imperato [124]. (C, D) Enhancement of electrically evoked dopamine release and dopamine efflux induced by methamphetamine in the nucleus accumbens core in acute brain slices *ex vivo*. (C) Representative superimposed voltammograms and current *vs* time evoked DA release (left and right). Baseline (green, left voltammograms), stimulation-induced dopamine release before (red) and after (blue) treatment of brain tissue with methamphetamine (voltammograms and current vs. time graph). (D) Representative voltammograms (1, 2

typical examples) of spontaneous dopamine efflux before (Meth(-)) and after 100 µM methamphetamine (Meth (+)) treatment. Modified from Hedges et al., 2018 [125].

Figure 3. Methamphetamine effects extending beyond inhibition of synaptic vesicles refilling at axon terminals. (A, B) Methamphetamine induced broadening of action potentials of nigral dopaminergic neurons resultant of the partial inhibition of potassium current. This effect is mimicked by the BK Ca^{+2} activated K^{+} current inhibitor paxillin. Adapted with permission from Lin et al., 2016 [97]. (C) Reduction of D_2/D_3 dopamine receptor availability in the basal ganglia of rats and human-caused by prolonged intake of methamphetamine. Representative structural MRI and autoradiography images using [^{125}I]-RTI-55 binding in control rats and rats receiving multiple doses of methamphetamine. Binding of DAT ligand [^{125}I]RTI-55 in a control rat and methamphetamine-treated rat (four doses of 4 mg/kg, with doses separated by 2 h intervals) revealed by autoradiography. Adapted with permission from O'Dell ey al., 2011 [126]. (D) A standard triaxial MRI of a human brain with the plane sampled images showing the locations of the caudate nucleus (Cd) and putamen (Put). A representation matching PET images acquired using the DAT ligand [^{11}C]WIN 35,428 in control subjects and in abuser of methamphetamine (21 times/month for 5.5 years). Adapted with permission from [127].

Table 1. Summary of experimental design and results of acute methamphetamine-induced changes in sleep parameters in humans and rhesus monkey studies.

Table 2. Summary of experimental design and results of changes in sleep parameters in humans and rhesus monkey studies by long-term methamphetamine use.

Table 3. Summary of the data on Intervention Trials with methamphetamine. Modified with permission from Paulus and Stewart [2].

TABLE 1: Summary of experimental design and results of methamphetamine-induced acute changes in sleep parameters (human and in rhesus monkey).

Reference	Subjects / N	Methods / Treatment / Readouts	Main Results
Perez et al., 2008	Methamphetamine users, n = 11	Intranasal administration, single dose (0, 12, 25, 50 mg/70kg); sleep questionnaire, psychomotor response	Objective and subjective measures: show sleep impairments at the largest doses
McGregor et al., 2005	Methamphetamine users, n = 21	Withdrawal (3 weeks of abstinence); AWQ self-report questioner, SMHSQ	Increase sleep latency; increase night-time, daytime and total sleep time; decrease sleep quality
Comer et al., 2001	Healthy volunteers, n = 7	Repeated oral intake, 5 or 10 mg; nightcap portable sleep monitors; self-inventory questionnaire	Disruptive effects on sleep based on subjective assessment; tolerance developed to drug effects
Kirkpatric et al., 2012	Healthy volunteers, n = 9	Repeated oral intake, 10 mg; oral (over 5 days); actiwatch; PSQI	Objective and subjective measures: show sleep impairments and tolerance develop
Kirkpatric et al., 2012	Healthy volunteers, n = 11	Repeated oral intake, 20, 40 mg (over 13 days). Sleep questionnaire, psychomotor response	Disruptive effects on sleep latency, delay in the sleep onset, reduction in relative and estimated hours of sleep
Ballard et al., 2015	Healthy volunteers, n = 60	Repeated oral intake, 0, 10, 20 mg, single time. Self- reported sleep quality; affective picture system	Disruptive effects on sleep with its delayed onset and poor quality in half of volunteers at the highest dose
Murnane et al. 2013	Rhesus monkeys, n = 5	Intramuscular injection of amphetamine; 0.1; 0.3 and 1.0 mg/kg; actiwatch	Dose-dependent increase of sleep latency, decrease of total sleep time
Berro et al., 2016	Rhesus monkeys, n = 5	Non-contingent priming (0.03, 0.1 and 0.3 mg/kg), i.v. followed by withdrawal; actiwatch	Sleep parameters unchanged but much improved during extinction compared to self-administration maintenance.
Berro et al., 2017	Rhesus monkeys, n = 5	Self-administration (0.01, 0.03 mg/kg) i.v. more than 5 consecutive days; actiwatch	Decreased sleep efficiency and increased sleep latency and sleep fragmentation.

TABLE 2: Summary of experimental design and results of sleep parameter due to long-term use and withdrawal effects of methamphetamine (human and rhesus monkey).

Reference	Subjects / N	Methods / Dose	Main Results
McGregor et al., 2005	Methamphetamine users, n = 21	Subacute withdrawal (over 2 weeks of abstinence); AWQ self-report questioner, SMHSQ	Low to moderate increase sleep latency; increase night- and daytime total sleep duration; decrease sleep quality
Mahoney 3rd et al., 2014	Methamphetamine users, n = 85	Long-term methamphetamine user; self-report questioners; PSQI, Epworth Sleepiness Scale (ESS)	Poor night sleep quality and enhanced daytime sleepiness; no correlation between PSQI or ESS scores with the age, education, years of drug use, dose
Tang et al., 2015	Methamphetamine users, n = 962	Long-term methamphetamine users; Self-report questionnaire; PSQI	Poor sleep quality (>50%), severe sleep problems (>30%). PSQI score correlated with duration of drug use
Mancino et al., 2011	Methamphetamine users, n = 6	Subacute methamphetamine withdrawal (over 4 weeks of abstinence); sleep inventory questionnaire	Increase sleepiness during 1st week; sleep quality decrease during 4 weeks of study
Herrmann et al., 2017	Drug experienced volunteers, n=19	Long-term recreational methamphetamine users; oral intake (0 or 20 or 40 mg); polysomnography; PSQI	Dose-dependent disruptions in sleep continuity and architecture; poor sleep quality in PSQI (>50%).
Andersen et al., 2013	Rhesus monkeys, n = 4	Long-term self-administration; 0.01-0.03 mg/kg, i.v.; actiwatch monitoring before, during and after administration.	Disrupted sleep efficacy, extended sleep latency; sleep fragmentation. Sleep normalized after drug discontinuation

TABLE 3: Summary of the data on intervention trials with methamphetamine [a].

Trials	Studies, No. (%)	
	All (n=159)	RCTs (n=65)
Trials with randomized intervention model		
With some results reported	25 (15.7)	25 (38.5)
Published	14 (8.8)	14 (21.5)
Studies with PMIDs		
No effect	8 (5.0)	8 (12.3)
Some effects	3 (1.9)	3 (4.6)
Unclear	3 (1.9)	3 (4.6)
Other studies		
No effect	5 (3.1)	5 (7.7)
Some effects	0	0
Unclear	6 (3.8)	6 (9.2)

Abbreviations: PMID, PubMed Reference number; RCTs, Randomized clinical trials.
[a] Registered at ClinicalTrials.gov that contained the term methamphetamine

Modified with permission from Paulus and Stewart 2020.

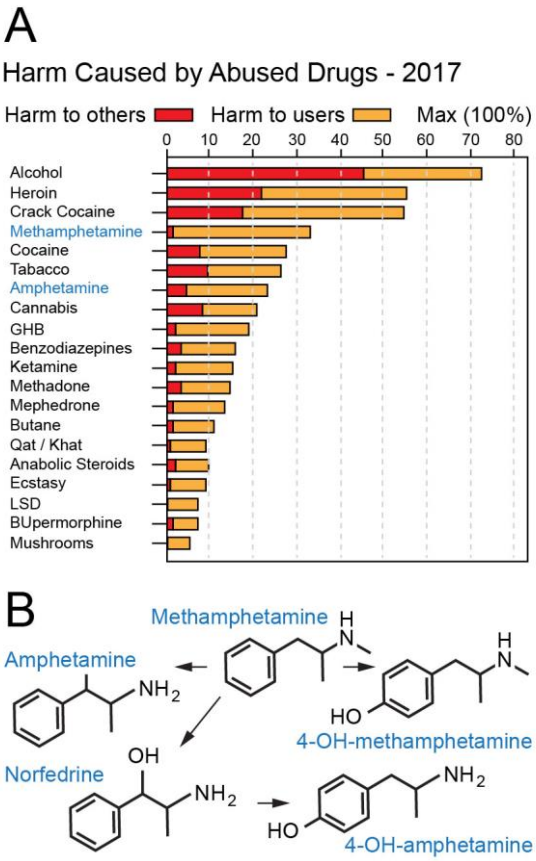

FIGURE 1

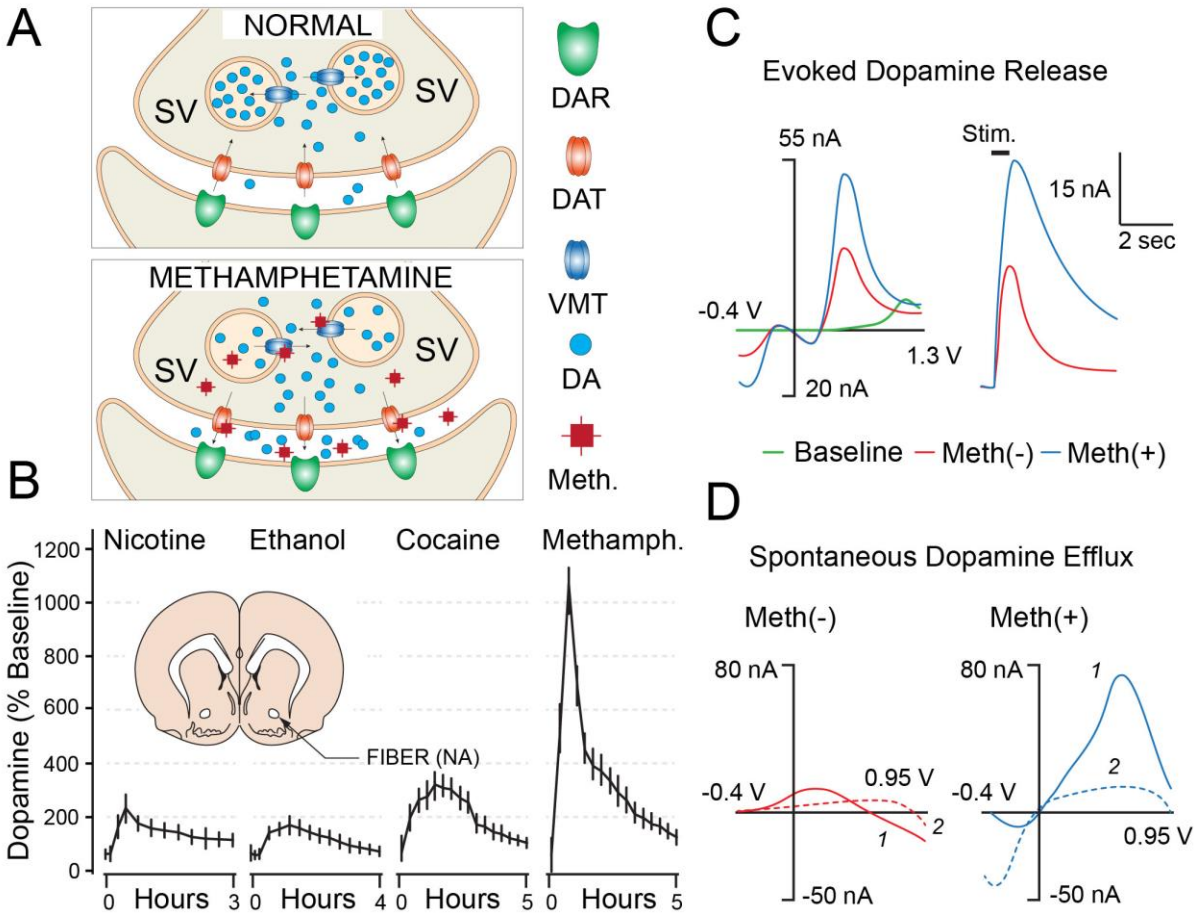

FIGURE 2

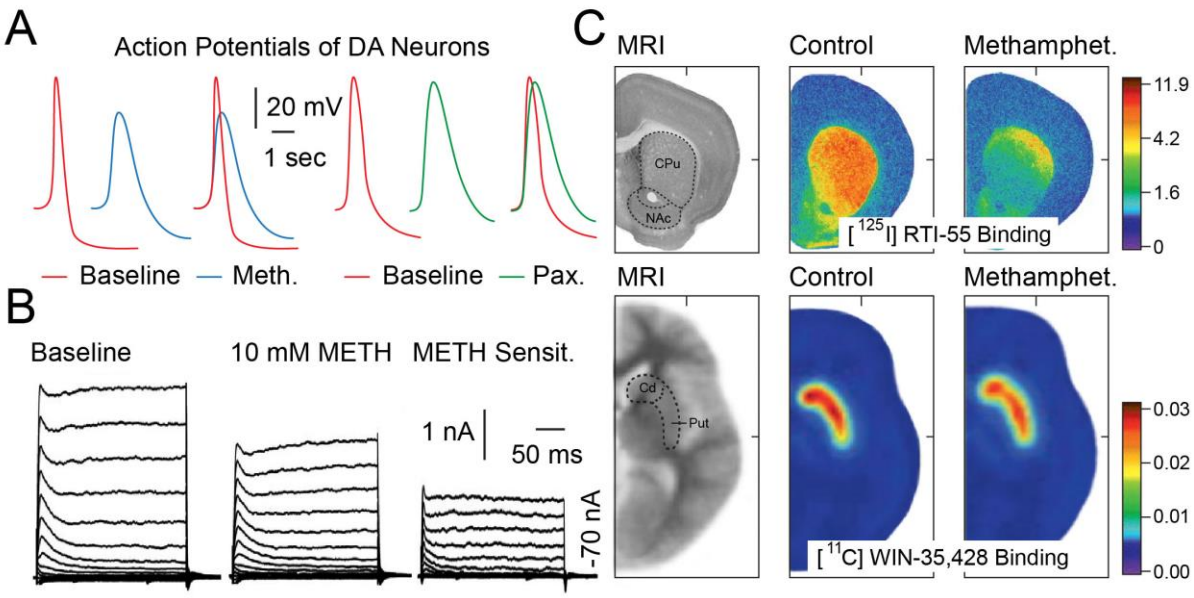

FIGURE 3