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Review

Evaluating Exercise as a Therapeutic Intervention for Methamphetamine Addiction-Like Behavior[1]

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Abstract. The need for effective treatments for addiction and dependence to the illicit stimulant methamphetamine in primary care settings is increasing, yet no effective medications have been FDA approved to reduce dependence [1]. This is partially attributed to the complex and dynamic neurobiology underlying the various stages of addiction [2]. Therapeutic strategies to treat methamphetamine addiction, particularly the relapse stage of addiction, could revolutionize methamphetamine addiction treatment. In this context, preclinical studies demonstrate that voluntary exercise (sustained physical activity) could be used as an intervention to reduce methamphetamine addiction. Therefore, it appears that methamphetamine disrupts normal functioning in the brain and this disruption is prevented or reduced by engaging in exercise. This review discusses animal models of methamphetamine addiction and sustained physical activity and the interactions between exercise and methamphetamine behaviors. The review highlights how methamphetamine and exercise affect neuronal plasticity and neurotoxicity in the adult mammalian striatum, hippocampus, and prefrontal cortex, and presents the emerging mechanisms of exercise in attenuating intake and in preventing relapse to methamphetamine seeking in preclinical models of methamphetamine addiction.

Keywords: Exercise, methamphetamine, addiction, animal models, reward, relapse, neurogenesis, neurotoxicity syndromes, neuronal plasticity

INTRODUCTION

For centuries, there has been widespread interest to understand the importance of physical activity on the overall quality of life of an individual. The idea that stress and mental states have adverse effects on physical health is well accepted, and conversely, it is suggested that a healthy body will espouse a healthy mind [3]. Thus, an emerging area of interest focuses on the mechanisms by which exercise (sustained physical activity) affects the mammalian brain, particularly on cognitive function. One way to conduct research in this field involves the use animal models to delve more deeply into cortical connectivity and molecular and cellular mechanisms involved in exercise and brain function. This micro-view allows us to see major benefits (and minor pitfalls) of exercise that may otherwise be easily overlooked.

Addiction or substance dependence is a mental disorder that involves the loss of behavioral control over drug taking and drug seeking which involves impulsivity and compulsivity. The impulsive and compulsive features of addiction can be grouped into three stages: [1] binge/prolonged intoxication, [2] withdrawal neutral/negative affect, and [3] preoccupation/anticipation (craving); these stages comprise the cycle of addiction. The limited (often recreational) use of drugs with abuse potential is distinct from the pattern of escalated drug use and the materialization of a chronic drug-dependent state [4]. Furthermore, the last stage of the addiction cycle describes a key element of addiction

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in humans which *defines* addiction as a chronic relapsing disorder [2]. Understanding the neurobiology of addiction is critical for identifying therapeutic strategies, and in this regard animal models of addiction have proved to be an immensely valuable tool for parsing out the neurobiological adaptations that contribute to the progression of addiction through these various stages [2, 5, 6].

A recent review detailed the value of exercise as a potential therapeutic strategy for intervention during the various stages of addiction for several drugs of abuse [7]. The therapeutic value of exercise could be due to its natural reinforcing effects and it may contribute to reward interaction, whereby, the presence of two reinforcing agents (e.g. illicit drug and exercise) could devalue the alternate reinforcer [8, 9]. The current review focuses on methamphetamine, a psychostimulant illicit drug with high abuse potential, with the objective to understand where the interaction between methamphetamine and exercise may be beneficial. This review discusses the neurobiological adaptations produced by exercise which contribute to reversing the negative effects of methamphetamine, in addition to exploring the theory of exercise itself eliciting addictive behavior.

METHAMPHETAMINE ADDICTION: IMPACT ON SOCIETY

The burden of methamphetamine abuse is increasing in the United States; available SAMHSA reports show 8% of all drug and alcohol treatment admissions involve methamphetamine and treatment studies report frequent relapses to methamphetamine seeking among those that are trying to quit [10]. Furthermore, methamphetamine abuse takes emotional and financial tolls on society, cutting across ages, races, ethnicities, and genders. It increases mortality, morbidity, and economic costs. Therefore, successfully reducing risk-taking behaviors, such as methamphetamine abuse, can potentially result in large public health gains [11, 12].

According to the recent reports from the National Institutes on Drug abuse (NIDA) and others, there are a few treatment options for methamphetamine addiction [1, 13–15]. For example, the best therapy currently available is the behavioral treatment approach (Matrix model, an outpatient treatment using psychosocial protocols, [16]); however, behavioral therapies are associated with lower beneficial effects on maintaining an individual's abstinence as well as reducing drug craving elicited by drug-related context and cues [17]. Therefore, NIDA is currently conducting research to seek improved treatment options, including investigating the efficacy of non-traditional and non-pharmaceutical options that may treat methamphetamine addiction.

PHYSICAL FITNESS VIA EXERCISE: IMPACT ON SOCIETY

In the world we live in today, almost everything we need is available at the click of a mouse. As an unfortunate consequence, it has become too easy to avoid physical activity and slip into a sedentary lifestyle, which has been associated with obesity, diabetes mellitus, increased risk of cardiovascular disease, and direct and indirect socioeconomic costs [18–21]. In recent years, the benefits of exercise on health and wellness have become increasingly well known. Exercise has been found to reduce the severity and even reverse the previously stated medical conditions associated with physical inactivity, which in turn reduces the cost of medical needs and other indirect socioeconomic costs [18, 22, 23]. Perhaps more relevant to this review, exercise can improve mental health by offering relief from the symptoms of depression and anxiety, and by improving mood [24–26]; these effects make exercise a valuable tool in disrupting the vicious feed-forward loop between mental illness and substance abuse [27–29].

While regular and regimented physical activity may be therapeutic, clinical cases of exercise eliciting addiction-like behavior have been reported with many sports activities including running, martial arts, weight lifting and body-building, and have been summarized in The Exercise Paradox [30]. The latter study used the Exercise Dependence Scale and the Exercise Addiction Inventory and reported that between 3.4% and 13.4% of a sample of university students were at high risk for "exercise addiction" [30]. Clinical cases have reported loss of control over exercise behavior and compulsivity or 'obligation' to perform exercise [30], both of which are hallmarks of addictive disorders [31]. Salience, withdrawal, emotional dysregulation, negative physical and psychosocial consequences, tolerance to the quantity and/or intensity, and relapse to abuse behavior are other phenotypes that support the notion that exercise may be an addictive behavior [30, 32–34]. However, because exercise is considered a sociologically normative behavior, *addiction to exercise* may be difficult to detect. Thus, partially due to the paucity of peer-reviewed evidence, "exercise addiction" is not yet categorized in Diagnostic and Statistical Manual of

Mental Diseases or International Classification of Diseases [31, 35]. Furthermore, excessive preoccupation with exercise has been observed with other disorders, including eating disorders and body dysmorphic disorders [33, 34, 36, 37]. This begs the question whether addiction-like exercise behavior is manifested due to vulnerability of specific personality types, or caused by excessive exposure to exercise. Animal models are more useful at parsing out such causalities.

EXERCISE AS A TREATMENT OPTION FOR METHAMPHETAMINE ADDICTION

In the context of substance abuse disorders, such as methamphetamine addiction, a single pharmacological intervention may not be sufficient or useful throughout the progression of addiction because the underlying neurobiology of addiction is continually changing between the different stages of addiction [2, 38]. Exercise is reported to have negative relationships with the extent, duration and frequency of drug use throughout the stages of initiation, prolonged intoxication, withdrawal, and relapse [7], and thus, has been sought out as a potential non-pharmacological treatment. Moderate exercise in methamphetamine dependent individuals significantly reduced depression symptom scores; in fact, "individuals with the most severe medical, psychiatric and addiction disease burden at baseline showed the most significant improvement in depressive symptoms by study endpoint" [39]. Similarly, group exercise for substance use disorder patients was found to significantly improve the physical health and psychological health domains of quality of life questionnaire; this intervention was beneficial even to patients with the most severe health problems [40]. Since depression and poor mental health are risk factors for relapse to drug seeking [27–29], these studies suggest that exercise is a useful strategy for reducing relapse in methamphetamine dependent individuals. Most importantly, the low cost and ease-of-implementation make exercise therapy all the more lucrative as a potential intervention. Therefore, clinical studies suggest that exercise can be used as a therapeutic intervention that may treat methamphetamine addiction, particularly during the relapse stage of addiction. The rest of the review will focus on the preclinical models of methamphetamine addiction and of exercise eliciting addiction like behavior. Furthermore, we hope to provide a brief overview on the neuroprotective effects of exercise on methamphetamine addiction in the context of inhibition of intake.

ANIMAL MODELS OF ADDICTION TO ILLICIT DRUGS

Drug-taking behavior has been demonstrated in rodent models of intravenous drug self-administration, in which rodents are trained to self-administer drugs by pressing a lever for an intravenous drug infusion in an operant conditioning chamber [41]. As mentioned previously, addiction is distinct from limited or recreational drug use. An increase in drug availability or a history of drug intake has been shown to accelerate the development of dependence in humans [42, 43]. Thus, animal models of addiction should highlight dependence-like behaviors, such as escalation of drug intake over time and withdrawal symptoms when the drug is withheld [41]. In that regard, intravenous methamphetamine self-administration with intermittent (1 h biweekly), limited (1 h daily), or long (extended; >4 h daily) access has significant clinical relevance by illustrating a range of different methamphetamine seeking behaviors in rats [44]. Extended access to methamphetamine produces an escalation of methamphetamine self-administration, suggesting compulsive drug intake and reflecting dependence-like behavior. Therefore, the escalation model may provide a useful approach to understand the neurobiological mechanisms responsible for the transition from limited methamphetamine use to compulsive intake. The escalation model may be particularly suitable for testing the hypothesis that alterations in adult brain plasticity induced by the methamphetamine are partially responsible for addictive behavior [41].

The reinstatement of drug-seeking behavior in rats is widely used as a model of craving that mimics the relapse stage of addiction often observed in the clinic [45], and is used extensively to uncover the key brain regions, brain circuitry, neurotransmitters, and neuromodulators associated with reinstatement behavior. The paradigm extinguishes learned self-administration behavior by explicitly not rewarding (e.g. withholding intravenous methamphetamine infusion) the animal after the correct response is emitted (e.g. a correct lever press) and tests the ability of a priming stimulus to reinstate drug-seeking response [46]. The stimuli can be cues previously paired with drug self-administration (cue priming) or acute noncontingent exposure to the drug (experimenter delivered; i.e., drug priming) or context (spatial location) where the drug was self-administered. The drug seeking reinstatement model has been used to mimic an addict's drug-response pattern [47], and mimic high rates of relapse [47, 48].

An alternative approach for assessing drug reward involves conditioned place preference (CPP), which determines the Pavlovian associations between rewarding effects of a drug and a contiguously presented stimulus, i.e. the context in which the rewarding effects of the drug are experienced [49, 50]. This conditioning approach is different from operant behavior, as it does not involve the animal 'working' for the drug reward (e.g. no lever responses), but rather, it examines the preference for the context following the development of the association [51]. Furthermore, in this model animals receive passive administration of the drug (i.e. experimenter delivered), and are tested (cue/context) in a drug-free state [50, 52]. Although the operant self-administration and CPP models have face validity, the operant model of drug reward and reinstatement is more advantageous. For example, while CPP behavior fails to demonstrate drug dose-dependency, the self-administration model is useful for eliciting distinct drug intake patterns (limited *vs*. compulsive intake of the drug) to mimic recreational use *vs*. dependent use, and to model an addict's drug-response pattern, and high relapse rates. Thus, the intravenous self-administration model of drug exposure appears to be the best suited for studying the neural mechanisms of drug reward and relapse.

ANIMAL MODELS OF SUSTAINED PHYSICAL ACTIVITY

Various animal models of exercise have been utilized which can be broadly classified as either voluntary or as forced exercise [53]. One of the most commonly used exercise paradigms involves the use of running wheels. In a voluntary wheel running paradigm, a wheel is placed in the home cage of the animal and the animal has *ad libitum* access to the wheel. In contrast, forced wheel running isolates the animal with the wheel and partitions off access to any other area; rotation of the wheel can be controlled remotely (using a computer or other mechanism) to ensure that the animal is forced to run while on the wheel [53]. Another forced exercise animal model is treadmill running, where the animal is forced to run on a motor-driven treadmill for a controlled amount of time [53]. Swimming has also been used as an exercise model where the animal was forced to swim in a tank with access to a platform for resting (optional) without leaving the water [54, 55]. Both voluntary and forced exercise paradigms have proven effective animal models; while voluntary exercise is typically chosen to simulate human choices for physical activity, forced exercise is suggested to more closely resemble human exercise regiments [56]. Environmental enrichment is another technique that provides greater opportunity for physical activity compared to standard housing conditions [53], but is a more complex paradigm with social and cognitive stimulation additionally involved; thus, environmental enrichment will not be discussed in the present review.

Utilizing these models of sustained physical activity, there is emerging evidence from animal studies that exercise is addictive and the behavioral outcomes can be compared with other drugs of abuse [8]. For example, the binge/intoxication phase of addiction is characterized by escalation of drug intake; in voluntary wheel running paradigms, escalation of running activity over days of access has been reported by several groups [57–60]. Such behavior indicates that exercise is reinforcing and can induce increased use over time. Additionally, using the CPP task, rats were reported to prefer the chamber previously paired with running wheels (wheel-paired context) compared to the chamber without wheel-pairing history [57], suggesting that access to running wheel is rewarding. Interestingly, physical exercise has been shown to activate the same mesolimbic reward pathway as illicit drugs; like methamphetamine, exercise can increase extracellular dopamine in the ventral striatum (Fig. 1), thus further identifying the neuronal mechanism underlying the rewarding and reinforcing effects of exercise [57, 61]. Combined, this body of research suggests that exercise is rewarding, and can illicit behaviors that correspond to the binge/intoxication phase of addiction.

The negative affect and withdrawal symptoms that are typical to drug dependence have also been observed in humans when experiencing a withdrawal from physical exercise [30]; some of these behavioral and physical aspects can also be found in animal models. For example, in mice that were selectively bred for high wheel running activity, providing access to running wheels and subsequently removing wheels access (withdrawal) lead to reduction of systolic and diastolic blood pressure, and of body temperatures, when compared with inbred mice with continued access to wheels or to control mice [62]. Evidence for the negative affect in animal models of drug addiction include behavioral symptoms such as depression and anxiety [63, 64]. Similar observations were made in exercise-preferring inbred mice that were withdrawn from running wheel activity, in whom behavioral despair or depression, assessed using the

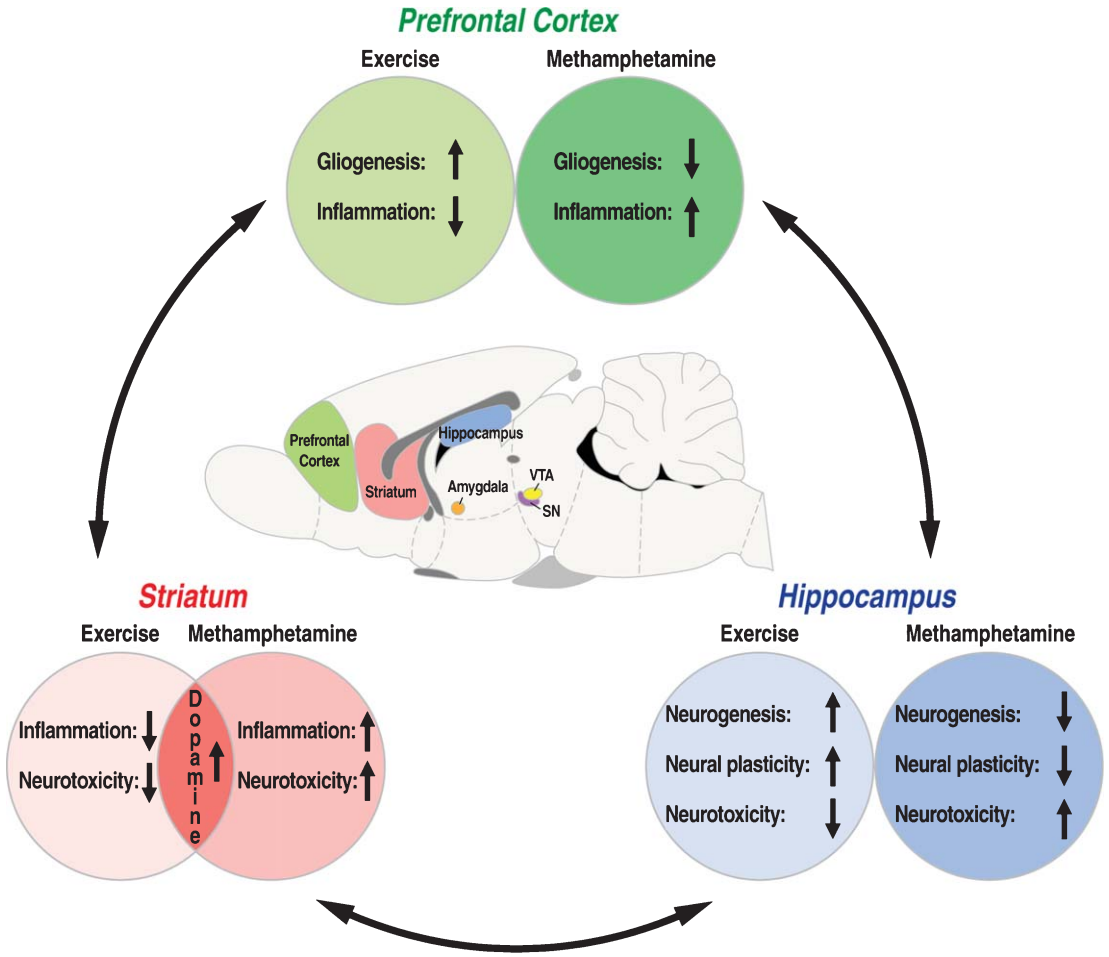

Fig. 1. Neurobiological Overlap of Methamphetamine and Exercise in the Adult Rodent Brain: A schematic for the overarching effects of methamphetamine and exercise on the reward, reinforcement and motivational centers of the adult rodent brain, particularly the prefrontal cortex (highlighted in green), the hippocampus (highlighted in blue), and striatum (highlighted in pink).

forced swim test, was elevated compared to control mice [65]. Taken together, animals that are genetically predisposed for high levels of physical activity and are then not permitted to engage in such activity, showed classical signs of withdrawal similar to those seen in drug dependent animals. However, these effects are not restricted to animals that are selectively bred for high wheel running. Outbred rats that were given free access to running wheels for 30 days and then prevented access to wheels for 24 hours were more likely to 'relapse' or binge on running after the wheels were reintroduced [60]. Because drug-addiction is a chronic relapsing disorder, the latter study provides strong evidence that, like drugs of abuse, running wheels can elicit relapse behavior. In conclusion, exercise does elicit addictive behavior, and this effect is enhanced in the genetically vulnerable strain.

CONVERGENCE BETWEEN EXERCISE AND METHAMPHETAMINE ADDICTION IN ANIMAL MODELS

There is an extensive amount of preclinical research supporting exercise as a treatment for drug addiction where exercise has been repeatedly shown to reduce the amount of drug intake during self-administration sessions (for review [7]). With respect to methamphetamine, exercise regimens have reduced self-administration during acquisition [58, 66] and during escalation of intake [58]. Research conducted in our laboratory also shows that access to exercise (voluntary wheel running) during protracted withdrawal from methamphetamine self-administration improved the rate of extinction and reduced both context- and cue-induced reinstatement of methamphetamine seeking [59]. Exercise also inhibits amphetamine reward

as evidenced by inhibition of CPP for amphetamine following forced treadmill running [67]. However, withdrawal from access to running wheels was found to increase methamphetamine intake during acquisition compared to rats with continued access to wheels as well as compared to exercise naïve rats [58]. Furthermore, escalation of methamphetamine intake did not differ between exercise-withdrawn rats and exercise-naïve rats [58], suggesting that the protective effect of exercise in methamphetamine addiction may be contingent on continued availability of the running wheel. This lends further credence to the hypothesis that the efficacy of exercise depends on its ability to serve as a strong alternate rewarding and reinforcing agent. The neurobiological bases underlying the effects of exercise in methamphetamine addiction as well as the adaptations underlying the addictive effects of exercise will be explored in the subsequent sections.

NEURAL CIRCUITRY UNDERLYING METHAMPHETAMINE AND EXERCISE ADDICTION

The reward and relapse circuitry in the adult mammalian brain has been delineated based on multiple groundbreaking studies performed in rodent models of acute and chronic reinforcement schedules and reinstatement to drug-seeking behavior [45, 68]. The acute reinforcing actions of stimulants, like methamphetamine, has been attributed to the mesolimbic dopamine pathway that initiates in the ventral tegmental area and terminates in the nucleus accumbens (ventral striatum; the brain reward center); however, it is important to note that for sedative/hypnotics and opiates, such as ethanol and heroin, these regions are not critical for the acute reinforcing effects [2]. Furthermore, there is evidence that neurotransmitters other than dopamine may also play a significant role in the rewarding effects of stimulants. For example, the nucleus accumbens receives inputs from several other brain regions, including the medial prefrontal cortex and hippocampal regions [2], and notably, the neurotransmitter glutamate from these regions regulates dopamine release from the nucleus accumbens and ventral tegmental area [69–71]. These results suggest that illicit drugs dysregulate prefrontocortical and hippocampal neurocircuitry, and thereby, contribute to the enhanced dopamine release from the mesolimbic dopamine pathway, and all of these regions play critical roles in the acute reinforcing effects of stimulant drugs [2].

The key brain regions implicated in the reinstatement of drug-seeking behavior include, but are not limited to, the medial prefrontal cortex, nucleus accumbens, bed nucleus of the stria terminalis, central nucleus of the amygdala, basolateral amygdala, hippocampal regions, and ventral tegmental area [2, 45, 68]. The dorsal striatum, that receives efferent projections from the mesocortical (the ventral tegmental area to prefrontal cortex) dopamine pathway, and the ventral striatum (nucleus accumbens) are considered the two focal points for reinstatement of drug-seeking behavior, or relapse centers of the brain [2, 68]. Most importantly, it is believed that the release of the neurotransmitters dopamine, glutamate, and corticotropin-releasing factor in these key brain regions are essential for the behavioral effects of the drug during the withdrawal and craving stages of addiction that contribute to relapse [72, 73]. The overlapping effects of exercise and methamphetamine on this neurocircuitry has been elegantly detailed in a recent review [7]; this overlap is briefly touched upon here from the perspectives of exercise addiction and of exercise therapy for methamphetamine addiction (Table 1).

To add to the existing theories on addiction, one recent discovery that is potentially important for addiction research is the ability of the adult mammalian brain to continuously generate new progenitors throughout adulthood. Broadly defined, progenitors are a progeny of stem cells that are characterized by limited self-renewal and can mature into differentiating cells, such as neurons and glia in the brain. The discovery [74–76] and eventual acceptance [77, 78] that adult-generated progenitors that can mature into neurons or glial cells in numerous mammalian species, including humans (for review [79]) has spurred substantial investigation of the proliferative capacity of brain regions such as the hippocampus. The role of adult neurogenesis in the hippocampus in methamphetamine addiction and the influence of exercise on these neural progenitors will be discussed in the subsequent sections.

NEURAL PROGENITORS AND NEUROGENESIS IN THE HIPPOCAMPUS IS AFFECTED BY METHAMPHETAMINE AND EXERCISE

Adult neurogenesis in the adult mammalian brain occurs in only one region of the hippocampus, namely the subgranular zone, situated on the border of the granule cell layer and hilus of the dentate gyrus. Stem-like precursor cells are mitotically active and divide

Table 1
Exercise and methamphetamine alter neurotransmission in the reward and reinforcement centers of the brain. This contributes to the value of exercise as a treatment for drug addiction (for review, [7, 245]). Of interest are dopaminergic and glutamatergic systems. The acute reinforcing actions of stimulants, like methamphetamine, has been attributed to the mesolimbic dopamine system that initiates in ventral tegmental area and terminates in the nucleus accumbens [2]. The transition of drug abuse behavior to prolonged intoxication and preoccupation/anticipation stage is accompanied by adaptations of the glutamatergic system [246, 247], which, in part, contribute to negative affect (example, depression and anxiety) during drug withdrawal [2]

Exercise	Methamphetamine and effect of exercise
Acute exercise activates mesolimbic dopamine pathway [57].	Methamphetamine increases extracellular dopamine in the brain by increasing release and reducing uptake [248, 249]. Exercise blunts the dopaminergic response to initial methamphetamine experience [250, 251].
Chronic running as well as predisposition for increased running induces dopaminergic adaptations [57, 252–254].	Chronic methamphetamine also produces neuroadaptations that lead to tolerance and hypofunctionalilty in the mesocorticolimbic dopamine pathway [255, 256]. This contributes to compensatory escalation of methamphetamine intake, and may further enhance relapse vulnerability.
A) Some of these adaptations may be beneficial.	A) Chronic exercise experience and continued access to exercise attenuated escalation of and relapse to methamphetamine self-administration [58, 59].
B) Some may be detrimental and contribute to escalation of exercise, particularly when exercise is withdrawn [57, 60].	B) Chronic exercise sensitized the reward system for other drug reinforcers, particularly when access to exercise is withdrawn [58, 60]
Increase expression of group II metabotropic glutamate receptors (mGluR2/3) in striatum, and dampen glutamate release and signaling in the striatum and the hippocampus [257–259]	Dysregulation of glutamatergic signaling, and internalization-mediated decrease of mGluR2/3 in the prefrontal cortex, nucleus accumbens and dorsal striatum is evidenced in methamphetamine escalation [260–262]. Activation of mGluR2/3 reduces methamphetamine seeking both before and after development of escalation [260]
Molecular markers associated with the negative affect and dependence, like increased ΔFosB and dynorphin were also found to be upregulated by exercise [263–265] withdrawal from exercise may result in the manifestation of negative affect [8, 62, 266].	Activation of mGluR2/3 in the nucleus accumbens during withdrawal from chronic methamphetamine administration is associated with depressive behavior [267]. Negative affect markers, ΔFosB and dynorphin, were upregulated by chronic methamphetamine [263, 268, 269], all of which may increase relapse risk.

into preneuronal progenitors (while simultaneously maintaining the stem-like population) which then differentiate into mature granule cells [80–82]. There is strong evidence that these cells not only functionally integrate into the hippocampal network [82–89], but also regulate hippocampal-sensitive cognitive function [90–100]. Further, the neurogenic properties of the dentate gyrus can be modulated by multiple factors, including physical activity and drugs of abuse [101, 102].

REGULATION OF HIPPOCAMPAL NEUROGENESIS BY METHAMPHETAMINE

The ability of methamphetamine to modulate proliferation and survival of hippocampal neural progenitors has not been as prolific of a research focus. Of the few studies investigating the deleterious impact of methamphetamine on dentate gyrus neuronal generation, both acute administrations [103, 104] and chronic exposures [105] reduce proliferation and survival of neural progenitors, although intermittent access to the drug appears to be unique in its enhancement of proliferation of progenitors [105, 106]. Further, findings from a recent cell cycle kinetic study (where newly born proliferating cells were sequentially labeled with mitotic markers to calculate the rate of movement of progenitors through the cell cycle) determined that the impairment of proliferation following chronic methamphetamine self-administration was the result of a reduction in number of S-phase progenitors (as opposed to a change in the length of S-phase of the cell cycle) [106]. With regards to hippocampal cognitive performance following methamphetamine self-administration, evidence demonstrates that performance on spatial and working memory tasks are inversely correlated to the quantity of methamphetamine consumed (operant self-administration) which also negatively correlates with hippocampal proliferation [107]. Interestingly, the survival of progenitors birth-dated at the start of the abstinent period was increased and positively correlated with reinstatement of methamphetamine seeking, thus implying a relationship between the survival of neural progenitors and the severity of relapse to the drug [107]. One potential mechanism for the impairments in hippocampal

granule cell proliferation is the observed dysregulation of the trophic factor brain derived neurotrophic factor (BDNF) and its receptor Tropomyosin receptor kinase B (TrkB), along with compromised glutamatergic signaling [108]. Taken together, these findings serve to support the theory that the neurogenic dysregulation caused by methamphetamine is an additional source of vulnerability to dependence on the drug [109–111].

REGULATION OF HIPPOCAMPAL NEUROGENESIS BY EXERCISE

Exercise exerts beneficial effects on hippocampal function and neurogenesis. Extensive evidence has demonstrated that exercise in animals is correlated with increases in both the number of neural progenitors as well as the number of surviving neurons in the hippocampus (for review, [56]). One of the mechanisms suggested for this increased neurogenesis is exercise-mediated increases in hippocampal trophic factors that are generally believed to support neuronal proliferation and survival, including BDNF and its receptor TrkB [112–128]. Other factors underlying the increased neurogenesis in the granule cell layer include increased stimulation and network activity in the surrounding hippocampus [115, 117, 119, 122, 124, 129–132], immune system regulation [133–136], and modulation of stress hormones [116, 137–140]. Furthermore, these increases in granule cell production correspond to improvements in hippocampal sensitive tasks including spatial navigation, pattern separation, and contextual fear conditioning (for review, [141]). Interestingly, evidence suggests that while the proliferative stimulation following exercise is lost relatively soon following cessation of activity, the increase in survival of granule cells continues for an extended duration, including into advanced age [58, 142]. Taken together, physical activity clearly enhances hippocampal neurogenesis and subsequently, hippocampal dependent cognition.

EXERCISE-INDUCED REDUCTION OF METHAMPHETAMINE TAKING AND SEEKING IS NOT ASSOCIATED WITH EXERCISE-INDUCED ENHANCEMENT OF HIPPOCAMPAL PROGENITORS AND NEUROGENESIS

It has been hypothesized that exercise-induced upregulation of hippocampal neurogenesis may underlie exercise-mediated reduction in the vulnerability to relapse in methamphetamine addicted animals [101]. However, recent findings demonstrate that wheel running-induced reduction in escalation of methamphetamine self-administration and reduction in reinstatement of methamphetamine seeking triggered by drug context and drug cues occurred independent of alterations in the number of neural progenitors and neurogenesis in the hippocampus [58, 59]. Therefore, while exercise and methamphetamine exert seemingly opposite effects on hippocampal neurogenesis (Fig. 1), the ability of exercise to regulate methamphetamine seeking appears to be dissociated from their effects of neurogenic events. Nevertheless, these studies have demonstrated that running activity during methamphetamine-self administration and during withdrawal prevented other measures of toxicity produced by methamphetamine (discussed below) to inhibit methamphetamine seeking behaviors [59].

METHAMPHETAMINE PRODUCES TOXICITY IN THE BRAIN

Studies over the past four decades have conceptualized that methamphetamine produces significant toxicity in the striatum, and that the neurotoxicity is responsible for the addictive effects of the drug. Briefly, methamphetamine reduces the function of dopamine transporters, vesicular monoamine transporters, tyrosine hydroxylase and MAO-B, to produce excessive dopamine release [143, 144] which leads to striatal neurotoxicity via enhanced reactive oxygen species (ROS) and reactive nitrogen species [145–157], and via compromised mitochondrial function [158, 159]. Methamphetamine also increases mitochondria-dependent pro-apoptotic proteins, decreases mitochondria-dependent anti-apoptotic proteins, and damages the endoplasmic reticulum, all of which contribute to increased neuronal cell death [159, 160]. Taken together, increased methamphetamine intake during extended access schedules of reinforcement leads to striatal neurotoxicity, which may be critical for the transition to compulsive use [161].

Non-striatal mechanisms have also been suggested for the emergence of the relapse/preoccupation anticipation stage of methamphetamine addiction [2]. Human imaging studies and postmortem studies provide converging evidence suggesting that chronic methamphetamine use produces neurotoxicity in the hippocampus [162, 163], and reduces frontal cortical, amygdalar, as well as hippocampal gray matter

volumes [164–170], all of which may underlie the profound deficits in executive function, declarative memory, and impulsivity in methamphetamine addicts [170–172]. The behavioral deficits observed in methamphetamine addicts have been demonstrated in preclinical models of binge methamphetamine exposure and extended access methamphetamine self-administration, where methamphetamine exposure produces cognitive dysfunction and memory impairments dependent on the hippocampus [48, 107, 173–176]. Neurodegeneration and neurotoxicity in the hippocampus is also observed, and positively correlated with methamphetamine-induced behavioral deficits [105, 177–179]. Additional mechanistic studies show that repeated methamphetamine exposure (via experimenter delivered paradigms) reduced the long-term potentiation of hippocampal CA1 pyramidal neurons [180, 181], increases excitability of dentate gyrus neurons [182], demonstrating that methamphetamine exposure produces synaptic maladaptation in the hippocampus that may mediate some of the addiction-dependent behaviors. Since long-term potentiation in CA1 and dentate gyrus regions positively and bi-directionally interacts with hippocampal neurogenesis [122, 130, 132, 183–185], methamphetamine-mediated altered plasticity in these regions may contribute to methamphetamine's effects on neurogenesis detailed in the section above.

Inflammation is another mechanism involved in methamphetamine-induced neurotoxicity, and its effects are considerably potentiated by oxidative stress [150]. Methamphetamine releases pro-inflammatory cytokines via activation of microglia and astroglia [186–188], which contribute to neuronal damage as well as behavioral deficits observed with chronic methamphetamine use [162, 189, 190]. Reduction in glial cell activation as well as administration of anti-inflammatory glial modulators have been found to reduce the sensitization to methamphetamine and methamphetamine self-administration in rodent models [191–194]. In conclusion, oxidative stress and associated mechanisms play a critical role in methamphetamine induced neurotoxicity and behavioral changes, which in turn further perpetuates maladaptive methamphetamine taking behavior.

PHYSICAL ACTIVITY REDUCES TOXICITY IN THE BRAIN

The previous sections have focused on the detrimental effects of ROS, however, it is important to understand that *moderate* levels of reactive species are in fact, beneficial and essential for cellular signaling, and epigenetic regulation [195]. Moderate levels of exercise regulates the body's redox homeostasis by improving metabolism and blood flow throughout the body, and that contributes to the several health promoting effects of exercise (for review [195]). Specifically, moderate exercise increases both antioxidant capacity and resistance against oxidative stress throughout the body, thus increasing resistance and tolerance to oxidative stress. Interestingly, the brain appears to be particularly protected against the adverse oxidative effects of over (or exhaustive)-exercise [196–199]. Specifically, the brain remained protected while skeletal muscles, liver and kidney showed oxidative damage following a single bout of exhaustive exercise; where the exercise paradigm involved treadmill running at 24 meters/min until the rat lost its righting reflex [196, 197]. Also, chronic exercise did not increase lipid peroxidation in the rat brain [198], although these effects are modulated by dietary vitamin intake [200, 201]. Compared to moderate training (swimming 1 hr/day for 8 weeks), very hard training (progressively increasing swim-time to 4.5 hr/day) and over-training (abruptly increasing swim-time from 1 hr/day to 4.5 hr/day) decreased brain protein oxidation products and improved performance in an associated rat memory task [199]; however, this tolerance has its limits as others report increased ROS and lipid peroxidation and impaired memory following intense or exhaustive exercise [202–204]. Exercise has been shown to exert beneficial effects in rodent models of several brain disorders including, but not limited to, models of ischemic stroke, stroke-prone spontaneously hypertensive rats and N-methyl-D-aspartate (NMDA) lesion models for Alzheimer's disease [205–207].

Several sub-cellular mechanisms are suggested to underlie the effects of exercise on brain function. These include increased expression of brain antioxidants including several superoxide dismutases, glutathione peroxidase and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) in the striatum and the hippocampus [208, 209]. The latter transcription factor, PGC-1α, is doubly beneficial as it can further upregulate other antioxidant enzymes, and more importantly, increase biogenesis of mitochondria to improve the efficiency of ATP generation, and thereby, reduce oxidative neurodegeneration in the substantia nigra and the hippocampus [210]. Exercise is also reported to increase the activity of proteasome complex in the brain [198], which is a putative mechanism for improved cognition and reduced

neurodegeneration in Alzheimer's Disease and Parkinson's Disease [211, 212].

Exercise, via modulation of oxidative pathways as well as through independent mechanisms, has been shown to modulate trophic factor signaling in the brain to promote brain plasticity (for review, [3, 213]). Specifically, exercise increases hippocampal BDNF expression, activates its downstream signaling pathways, and increases cAMP response element binding protein (CREB), that subsequently upregulates other inducible transcription factors [214–216]. These molecular changes could manifest themselves as beneficial neuroplasticity changes such as increasing cell survival [217, 218], formation of new synapses (synaptogenesis; [219]), and neurogenesis [220, 221]. Furthermore, because ROS is known to dose-dependently modulate proliferation of neuronal progenitor cells in the hippocampus [217, 222], exercise may modulate neurogenesis by regulating ROS in the dentate gyrus. Modulating the levels of trophic factors and ROS in regions other than the dentate gyrus may alter the generation of new glia (gliogenesis), such as astroglia and oligodendroglia that may contribute to functional plasticity [222–225]. The medial prefrontal cortex, a brain region involved in executive and impulse control [38, 226, 227], is one region where this mechanism has been investigated [44]. Specifically, voluntary wheel running in rats was also shown to increase in proliferation and survival of progenitor cells medial prefrontal cortex, and these new cells matured into new astroglia (∼33%) and new oligodendroglia (∼55%) [44]. Thus, exercise-induced gliogenesis may be a mechanism underlying exercise-induced improvement in cognition and executive function observed in several disease conditions [228, 229].

EXERCISE-INDUCED REDUCTION OF METHAMPHETAMINE TAKING AND SEEKING IS ASSOCIATED WITH EXERCISE-INDUCED REDUCTION OF METHAMPHETAMINE-INDUCED BRAIN TOXICITY

As discussed previously, exercise reduces methamphetamine intake when both the reinforcers are concurrently available, in part, because exercise serves as an alternative reinforcer ([7]; also see Table 1). However, the above sections demonstrate that the potential for overlap between exercise and methamphetamine extends much deeper and is more complicated than simply modulating neurotransmission in the brain reward and reinstatement centers (Fig. 1). Exercise improves brain function via changes in redox homeostasis and contributes to increased resistance and tolerance to oxidative challenge, and thereby promotes cell survival. Notably, swimming exercise was found to attenuate amphetamine-induced CPP and anxiety, which corresponded with exercise-induced reduction in ROS and protein oxidation products in hippocampal homogenates [54]. Studies conducted by our group and others revealed that rats with continued access to voluntary wheel running attenuated acquisition and escalation of methamphetamine self-administration compared to rats without access to running wheels [58, 66]. Furthermore, access to running wheels during protracted abstinence from methamphetamine accelerated extinction and attenuated reinstatement of methamphetamine seeking [59]. Indeed, voluntary running attenuated methamphetamine-induced damage to dopamine and serotonin terminals in the striatum, potentially, by promoting repair of the damaged terminals [230, 231]. Further, attenuated methamphetamine self-administration in rats with continued access to voluntary wheel running was associated with attenuation of neuronal apoptosis and decreased neuronal nitric oxide synthase expression in the nucleus accumbens [58], suggesting that regulation of oxidative stress mechanisms may be an alternate or concomitant mechanism which contributes to the beneficial effects of exercise in methamphetamine addiction. Future studies should include empirical validation of these mechanisms in exercise-mediated modulation of methamphetamine seeking.

Interestingly, withdrawal from wheel running during methamphetamine self-administration enhanced consumption of methamphetamine compared to exercise-naïve rats [58], suggesting that deprivation from chronic exercise may render subjects vulnerable to methamphetamine. The latter observation further contributes to the idea that exercise itself is addictive, however, very little is known about the mechanism underlying this increased addiction vulnerability. Evidence from studies in mice selectively bred for increased voluntary wheel running suggests dopamine is increased in the nucleus accumbens and the dorsal striatum (the reward and reinforcement centers of the brain), but is negatively correlated with running suggesting attenuation of sensitivity to reinforcing effects of running [232]. Furthermore, the dorsal striatum and substantia nigra were hypo-dopaminergic [233] thus providing a conducive environment for mechanisms that can compensate for this reduced dopamine tone (for example, methamphetamine-induced dopamine

release; Table 1). Finally, running correlated with hippocampal activation (increased Fos) in controls but this correlation was lost in mice selectively bred for high wheel running activity [234]. Instead, the high runners showed increased activation (Fos) of the motivation circuitry, i.e. prefrontal cortex, striatum and lateral hypothalamus along with increased BDNF in the hippocampus [234, 235]. Taken together, a blunted dopamine reward system, a hypodopaminergic response in the nigro-striatal pathway (relapse circuitry) together with the activation of neurons in the brain regions involved in motivation in the exercise-withdrawn animal, may contribute to the addictive effects of exercise and may provide the ideal environment for cross-sensitization to other powerful reinforcers such as methamphetamine. However, these speculations need to be empirically validated using animal models.

FUTURE DIRECTIONS AND CONCLUSION

While some information is available regarding the associated neurobiological changes underlying the interactions of exercise with methamphetamine taking and seeking, a lot of the potential mechanisms have not been empirically evaluated. An example, is the opposite effects of methamphetamine and chronic exercise on astrocytes and inflammatory markers in the brain [186, 187, 236, 237], and yet their interaction in these avenues remains unexplored. Furthermore, there is a gap in our understanding of the neurobiological adaptations following exercise withdrawal and neurobehavioral effects of excessive exercise. An emerging direction in drug abuse research investigates epigenetic modifications of the chromatin structure that results in activation or repression of gene expression in altering the vulnerability to drug addiction [238, 239]. Epigenetic modification not only alters the rewarding effects of methamphetamine, chronic methamphetamine also produces epigenetic changes that are permissive for progressing through the different phases of addiction [240, 241]. Particularly, modifications in the genes regulating BDNF expression and signaling have been implicated in the initiation-binge/intoxication stage as well as the relapse-preoccupation/anticipation stage of psychostimulant addiction (for review, [242]). Exercise is known to increase BDNF expression in the hippocampus [243], and epigenetic modifications have been shown to be a part of the underlying mechanism [244]. It would be interesting to see how epigenetic modifications by exercise lead to long-term adaptations that promote/inhibit methamphetamine taking and seeking.

In sum, the identification of the neuroplastic and neuromodulatory effects of exercise over the past few decades has shed new light on the therapeutic and, more recently, the protective effects that are associated with exercise. Future studies aimed at understanding the potential link between correlative decreases in illicit drug use and addiction and increase in exercise output in animal models will allow researchers to determine whether decreases in neurotoxicity by exercise is behaviorally relevant to the prevention of addiction to illicit drugs. This may pave the way for future therapeutic possibilities for treating drug addiction disorders.

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