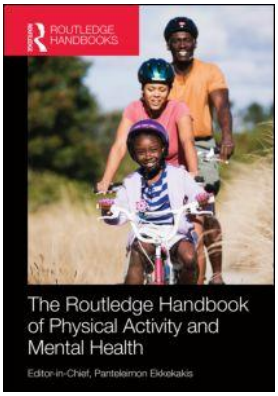

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THE NEUROBIOLOGY OF EXERCISE AND DRUG-SEEKING BEHAVIOR

Mark A. Smith and Wendy J. Lynch

Epidemiological studies consistently report that physical activity is inversely related to substance use and abuse. Similar to many abused substances, physical activity produces positive affective states in both humans and animals. These positive affective states can be measured objectively and quantitatively, and have been demonstrated under a variety of experimental conditions (Belke & Wagner, 2005; Greenwood et al., 2011; Janal, Colt, Clark, & Glusman, 1984; Lett, Grant, Byrne, & Koh, 2000; Lett, Grant, & Koh, 2001; Nabetani & Tokunaga, 2001). Exercise also functions as a positive reinforcer, in that both humans and animals will perform an operant response (e.g., drive to a gym, press a lever) in order to engage in physical activity (Belke, 1997, 2000; Belke & Dunbar, 2001; Iversen, 1993; Schebendach, Klein, Foltin, Devlin, & Walsh, 2007). Preclinical studies report that aerobic exercise decreases drug self-administration and other measures of drug-seeking behavior. For instance, in laboratory rats, access to a running wheel decreases the acquisition (Smith & Pitts, 2011), maintenance (Cosgrove, Hunter, & Carroll, 2002; Smith, Schmidt, Iordanou, & Mustroph, 2008), and escalation (Smith, Walker, Cole, & Lang, 2011) of cocaine self-administration, and decreases the reinstatement of cocaine-seeking behavior after a period of abstinence (Lynch, Piehl, Acosta, Peterson, & Hemby, 2010; Smith, Pennock, & Walker, 2011; Zlebnik, Anker, Gliddon, & Carroll, 2010). Similar effects have been reported with other drugs of abuse, including alcohol (Crews, Nixon, & Wilkie, 2004; Ehringer, Hoft, & Zunhammer, 2009, but see Werme, Lindholm, Thorén, Franck, & Brené, 2002; McMillan, McClure, & Hardwick, 1995; Ozburn, Harris, & Blednov, 2008), morphine (Hosseini, Alaei, Naderi, Sharifi, & Zahed, 2009), and methamphetamine (Miller et al., 2011). A number of behavioral/psychological mechanisms likely contribute to the beneficial effects of exercise on drug-seeking behavior. For instance, exercise decreases several comorbid psychological conditions that are associated with substance abuse and dependence. Specifically, exercise decreases measures of depression and anxiety (see reviews by Herring, O'Connor, & Dishman, 2010; Perraton, Kumar, & Machotka, 2010), both of which are risk factors for developing a substance use disorder (Castle, 2008; Swendsen & Merikangas, 2000). Exercise also reliably increases measures of well-being, self-esteem, and self-efficacy (Fillipas, Oldmeadow, Bailey, & Cherry, 2006; Hughes et al., 2010; Muller et al., 2008). These positive psychological states are negatively correlated with substance use (Ellickson & Hays, 1991; Griffin, Scheier, Botvin, & Diaz, 2001; Zamboanga, Schwartz, Jarvis, & Van Tyne, 2009), and may offer protection against developing a substance use disorder. In addition to these mechanisms, exercise also produces functional adaptations in

the central nervous system that may leave an individual less susceptible to developing compulsive patterns of drug intake. Although research into this latter area is still in its infancy, a growing number of studies reveal that many signaling molecules that mediate drug-seeking behavior are modulated by physical activity.

Dopamine

The mesolimbic reward pathway, which includes dopaminergic (DAergic) projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and prefrontal cortex (PFC), is believed to play a critical role in addiction, with results from numerous studies showing that many drugs of abuse, including cocaine, amphetamine, nicotine, alcohol, and opioids, increase extracellular DA in the NAc (Leshner & Koob, 1999). Five dopamine receptors, D1–D5, have been identified and further classified into two receptor subtypes: the D1 class, which includes the D1 and the D5 receptor subtypes, and the D2 class, which includes the D2, D3, and D4 receptor subtypes. The D1 class of receptors couple with stimulatory G proteins, which activate 3'–5'-cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA), whereas the D2 class of receptors couple with inhibitory G proteins and have the opposite effects on cAMP and PKA. Pharmacological manipulation of DA via either D1 or D2 receptor blockade in the NAc is known to modulate responding for drugs of abuse, including cocaine, alcohol, and heroin (Cornish, Lontos, Clemens, & McGregor, 2005; Hodge, Samson, & Chappelle, 1997; McGregor & Roberts, 1993; Robledo, Maldonado-Lopez, & Koob, 1992). Evidence also suggests that enhanced DA signaling is involved in drug-seeking behavior. The neurobiology is best described for reinstatement of cocaine-seeking behavior, and results show that both D1 and D2 receptors play a critical role. Systemic pretreatment with D2 receptor antagonists inhibits cocaine-seeking behavior (Schenk & Gittings, 2003), whereas systemic pretreatment with D2 receptor agonists reinstates responding and potentiates cocaine-primed reinstatement (Self, Barnhart, Lehman, & Nestler, 1996). Systemic pretreatment with D1 receptor antagonists blocks reinstatement, and systemic pretreatment with D1 receptor agonists produces similar effects (Self et al., 1996). Fewer studies have examined the role of D1 and D2 receptor signaling for other drugs, but the available results for heroin (Bossert, Poles, Wihbey, Koya, & Shaham 2007; Shaham & Stewart, 1996), nicotine (Liu et al., 2010), and alcohol (Chaudhri, Sahuque, & Janak, 2009; Liu & Weiss, 2002) are similar to the results obtained with cocaine, suggesting that DAergic signaling is critically involved in mediating drug seeking and relapse for many drugs of abuse.

Exercise impacts DAergic signaling under many experimental conditions. For example, exercise increases the transport of calcium into the brain where it activates the synthesis of DA (Sutoo & Akiyama, 1996). Exercise also increases mRNA levels of tyrosine hydroxylase, the rate-limiting enzyme in DA synthesis, in the VTA and other brain regions (Greenwood et al., 2011). Exercise increases DA concentrations in numerous brain regions (Dishman, 1997), with recent evidence showing that animals selectively bred for high rates of wheel running have higher basal and exercise-induced concentrations of DA and DA metabolites and lower DA turnover in the NAc and striatum as compared with controls (Mathes et al., 2010). Exercise also normalizes DAergic signaling in the striatum and NAc of animals that have abnormally low levels of dopamine (e.g., epileptic mice, spontaneously hypertensive rats) by facilitating calcium/calmodulin-dependent DA synthesis (Sutoo & Akiyama, 2003). At the receptor level, chronic exercise, like chronic exposure to drugs of abuse, downregulates DA D2 receptors, with recent evidence showing that DA D2 receptor mRNA is reduced in the NAc of rats following chronic voluntary exercise (Greenwood et al., 2011). Similarly, transcripts encoding for both the D1 and D2 receptor genes are downregulated in the striatum of mice bred for high levels of running as

compared with controls (Mathes et al., 2010). Recent data also indicate that pre-exposure to aerobic exercise blocks methamphetamine-induced conditioned place preference (Chen et al., 2008), methamphetamine-induced increases in DA release in the NAc (Chen et al., 2008), and amphetamine-induced DA release in the striatum (Marques et al., 2008). Collectively, these data show that exercise affects DA levels, synthesis, and metabolism, as well as DA receptor-mediated signaling. These data also suggest that exercise may interact with the reward pathway by serving as a substitute for drug reward, and may protect against drug relapse by countering neuro-adaptations in DAergic signaling that develop following chronic drug exposure.

Glutamate

Glutamate is the main excitatory neurotransmitter in the NAc, and it activates two ionotropic receptors: the N-methyl-D-aspartate (NMDA) receptor and the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor. Although acute exposure to drugs of abuse does not generally alter glutamate release in the NAc, repeated administration decreases basal levels of glutamate and increases glutamate in response to subsequent drug exposure, suggesting that its role in mediating the reinforcing effects of drugs may become greater with repeated exposure (Schmidt & Pierce, 2010). Numerous studies have shown that chronic drug exposure produces long-lasting adaptations in glutamate receptors, including NMDA and AMPA receptors in the NAc and PFC of humans, non-human primates, and rats (Acosta et al., 2010; Hemby et al., 2005; Tang, Wesley, Freeman, Liang, & Hemby, 2004), as well as long-term decreases in AMPA receptor signaling (Beurrier & Malenka, 2002). Based on such findings, it has been suggested that glutamatergic projections from the PFC to the NAc represent a final common pathway toward the generation of drug-seeking and relapse (Kalivas & Volkow, 2005). Evidence in support of this idea is supported by findings showing that glutamate is increased in the NAc in response to both drug primes and drug-associated cues (Kalivas & McFarland, 2003), and by results showing that glutamate receptor antagonism in the NAc, particularly via AMPA receptors, attenuates drug-seeking behavior (Bäckström & Hyytiä, 2007; Cornish, Duffy, & Kalivas, 1999). Together, these findings suggest that adaptations in glutamatergic signaling modulate drug use following chronic administration and subsequent drug-seeking behavior.

Although few studies have examined the effects of exercise on glutamatergic signaling in the reward pathway, results from numerous studies show that it can affect glutamate signaling in several different areas in the brain. Most of the results have been obtained from animal models of cerebral ischemia, which results from the excessive release of glutamate and overstimulation of glutamate receptors, with results showing that exercise can normalize glutamate levels and improve functioning. Within the striatum, exercise blocks the increase in glutamate caused by ischemic injury (Jia et al., 2009). This result is important because it suggests that exercise may protect against overstimulation of glutamatergic receptors, which also occurs following chronic drug exposure. In non-ischemic "normal" animals, chronic exercise increases extracellular glutamate concentrations (Chang, Yang, Wang, & Wang, 2009) and AMPA receptor density (Dietrich et al., 2005; Real, Ferreira, Hernandes, Britto, & Pires, 2010) in the striatum. Exercise also increases striatal fos expression (a marker of functional activity), and this effect can be blocked by concurrent activation of NMDA and D1 receptors (Liste, Guerra, Caruncho, & Labandeira-Garcia, 1997). These findings suggest that the effects of exercise on reinstatement may involve both DAergic and glutamatergic signaling.

Norepinephrine

Norepinephrine plays an important role in drug-seeking behavior, particularly in later transitional stages that involve relapse to drug use after a period of abstinence. Preclinical studies have reported that norepinephrine is important for both stress-induced and cocaine primed-reinstatement (Erb et al., 2000; Léri, Flores, Rodaros, & Stewart, 2002; Zhang & Kosten, 2005). Stress-induced reinstatement is mediated by activation of beta-adrenergic receptors in the amygdala and bed nucleus of the stria terminalis (Erb et al., 2000; Léri et al., 2002), whereas cocaine-primed reinstatement is mediated, in part, by activation of alpha1-adrenergic receptors (Zhang & Kosten, 2005). Exercise decreases norepinephrine release in the frontal cortex (Soares et al., 1999), which may serve to attenuate the effects of stress and cocaine in reinstatement procedures. The mechanism by which exercise influences noradrenergic activity is not fully known, but the peptide neurotransmitter galanin is believed to play a role. Galanin is co-localized with norepinephrine in locus coeruleus neurons, and there is extensive galaninergic innervation of limbic and forebrain areas (Holets, Hökfelt, Rökaeus, Terenius, & Goldstein, 1988; Melander, Staines, & Rökaeus, 1986; Xu, Shi, & Hökfelt, 1998). Activation of G protein-coupled galanin receptors inhibits the firing of locus coeruleus neurons (Ma et al., 2001; Pieribone et al., 1995) and potentiates the inhibitory effects of norepinephrine at presynaptic alpha-2 adrenergic autoreceptors (Ma et al., 2001). Importantly, physical activity increases galanin gene expression in locus coeruleus neurons (O'Neal, Van Hoomissen, Holmes, & Dishman, 2001; Van Hoomissen, Holmes, Zellner, Poudevigne, & Dishman, 2004), and exercise output is positively correlated with levels of prepro-galanin mRNA (Eisenstein & Holmes, 2007; Holmes, Yoo, & Dishman, 2006). Thus, galanin-mediated decreases in norepinephrine signaling may be one way in which exercise decreases drug-seeking behavior in reinstatement procedures.

Opioids

Exercise increases plasma concentrations of endogenous opioid peptides. Studies have consistently reported increases in the mu- and delta-receptor ligands, beta-endorphin, met-enkephalin, and leu-enkephalin (Art, Franchimont, & Lekeux, 1994; Chen, Zhao, Yue, & Wang, 2007; Debruille et al., 1999) and the kappa-receptor ligand, dynorphin (Aravich, Rieg, Lauterio, & Doerries, 1993; Fontana et al., 1994) following aerobic activity. The positive affective states produced by exercise are blocked by the opioid antagonist naloxone (Lett et al., 2001), indicating that these effects are mediated by opioid receptors. Long-term exercise produces alterations in opioid binding proteins (de Oliveira et al., 2010; Houghten, Pratt, Young, Brown, & Spann, 1986) and decreases sensitivity to exogenously administered opioid agonists (Kanarek, Gerstein, Wildman, Mathes, & D'Anci, 1998; Mathes and Kanarek, 2001; Smith & Lyle, 2006; Smith & Yancey, 2003). In drug self-administration studies, voluntary wheel running decreases heroin self-administration (Smith & Pitts, 2012) and forced exercise on a treadmill decreases morphine self-administration (Hosseini et al., 2009). Reductions in the positive reinforcing effects of heroin and other opioids are likely mediated by changes in central opioid receptor populations following chronic exercise. Changes in opioid receptor populations may also play a role in the ability of exercise to decrease the self-administration of other drugs. Studies have shown that the opioid receptor system plays an important modulatory role in the reinforcing effects of cocaine (Herz, 1998; Mello & Negus, 2000) and alcohol (Roberts et al., 2000, 2001; Walker, Zorrilla, & Koob, 2011), and the kappa opioid receptor system is critically involved in the escalation of cocaine intake under extended-access conditions (Wee & Koob, 2010). Release of endogenous opioid peptides may thus be one way exercise produces generalized protective effects on drug-seeking behavior across multiple pharmacological classes.

PKA

Chronic exercise and chronic exposure to drugs of abuse produce a number of changes in second-messenger signaling systems. For example, chronic cocaine upregulates D1-cyclic adenosine monophosphate (cAMP)-PKA signaling, and the reinforcing capacity of various D1 agonists is positively correlated with their ability to stimulate cAMP production (Weed, Paul, Dwoskin, Moore, & Woolverton, 1997). Direct activation of PKA increases the reinforcing effects of drugs of abuse such as cocaine (Lynch & Taylor, 2005, but see Self et al., 1998), whereas inhibition of PKA decreases both motivation for the drug and subsequent drug-seeking behavior (Lynch and Taylor, 2005; Sanchez, Quinn, Torregrossa, & Taylor, 2010). Upregulation of PKA has been reported following both chronic high-dose cocaine administration (Terwilliger, Beitner-Johnson, Sevarino, Crain, & Nestler, 1991) and extended-access cocaine self-administration (Lu, Grimm, Shaham, & Hope, 2003; Lynch, Kiraly, Caldarone, Picciotto, & Taylor, 2007), but not following less intense chronic cocaine-treatment protocols (e.g., Crawford, Choi, Kohutek, Yoshida, & McDougall, 2004). Exercise also influences DAergic signaling via second-messengers, with results showing that mice bred for high levels of running have lower levels of the transcripts encoding for several different adenylate cyclase subtypes and activating polypeptides in the striatum, as compared with controls (Mathes et al., 2010). Exercise also modulates intracellular signaling proteins associated with DA-mediated signaling, including dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32) (Aguiar et al., 2010), a well-known target of PKA that is essential for drug reinforcement (Svenningsson, Nairn, & Greengard, 2005).

Extracellular signal-regulated kinase

Extracellular signal-regulated kinase (ERK) is a molecule that is a key mediator of synaptic plasticity and is modulated by both drugs of abuse and exercise. ERK, which requires coincident activation of DA D1 and glutamate NMDA receptors, is critically involved in drug craving and relapse (Thomas, Kalivas, & Shaham, 2008). Specifically, levels of ERK in the NAc and projection sites of the NAc, including the PFC and amygdala, are correlated with levels of drug seeking across several different drug classes, including cocaine (Edwards, Bachtell, Guzman, Whisler, & Self, 2011; Koya et al., 2009; Lu, Koya, Zhai, Hope, & Shaham, 2006; Lynch et al., 2010), alcohol (Schroeder et al., 2008), and morphine (Li et al., 2008). Furthermore, like levels of drug-seeking behavior, phosphorylated levels of ERK increase over an abstinence period (Edwards et al., 2011; Kim & Kim, 2008; Koya et al., 2009; Li et al., 2008; Lu et al., 2006). Although very little is known with regard to the effects of exercise on ERK signaling in the NAc or PFC, there is a large literature indicating regulation of ERK by exercise in other brain regions and in peripheral tissue (muscle, heart; e.g., Kojda & Hambrecht, 2005; Smith & Zigmond, 2003). ERK contributes to long-term potentiation and regulates various learning tasks such as conditioned place preference, and both exercise and exposure to cocaine-associated cues upregulate phosphorylated levels of ERK in the hippocampus (Muller et al., 2008). There is also evidence to suggest that ERK activation is critical for the beneficial effects of exercise on mood (Gourley et al., 2008), raising the possibility that exercise may counter dysphoric mood states associated with drug withdrawal. Finally, a recent study reported that exercise attenuates cocaine-seeking behavior and blocks the increase in phosphorylated levels of ERK associated with enhanced cocaine seeking (Lynch et al., 2010). These findings suggest that exercise may reduce relapse vulnerability by preventing the increase in cocaine craving and associated neuroadaptations in ERK signaling.

Brain-derived neurotrophic factor

Synaptic changes occurring via brain-derived neurotrophic factor (BDNF) have also been implicated in drug addiction and are modulated by exercise. BDNF is synthesized in VTA DA neurons and enhances both DAergic and glutamatergic signaling (Blöchl & Sirrenberg, 1996; Lessman, 1998). Levels of BDNF increase incrementally in the reward pathway (i.e., VTA, NAc, and amygdala) over an abstinence period and are associated with progressive increases in drug-seeking behavior (i.e., Grimm et al., 2003). Exercise elevates BDNF, and through epigenetic mechanisms can modulate the chromatin structure containing the BDNF gene (Gomez-Pinilla, Zhuang, Feng, Ying, & Fan, 2011). Given that long-term changes in synaptic plasticity involving BDNF are strongly implicated in drug addiction, it is possible that exercise may be able to normalize some of these synaptic changes and reduce subsequent relapse vulnerability.

Other molecules

Evidence supports the effects of exercise on other signaling pathways (e.g., gamma-aminobutyric acid (GABA), serotonin, endocannabinoid, cortisol), but fewer studies have examined such pathways in the context of both exercise and drug-seeking behavior. Research on these systems will continue to expand, and it is likely that this research will show that exercise influences these molecules in ways that impact drug self-administration. Importantly, receptor-specific ligands are already available in most instances, which should expedite research into their role in drug abuse, as well as their modulation by physical activity.

Conclusions

Recent research has revealed that many signaling molecules associated with compulsive patterns of drug intake are influenced by physical activity. These findings represent a significant advancement in our understanding of the neurobiological effects of exercise, and contribute greatly to our understanding of the neurobiology of substance abuse and dependence. Additional research is still needed to determine which of these various molecules are related causally to the protective effects of exercise on drug-seeking behavior. Studies that target individual proteins through site-specific antagonists, genetic knockouts/knockdowns, and antisense oligonucleotides should determine which neurotransmitters and intracellular signaling molecules are mediating this relationship. Future research in this area will aid in the development of behavioral and pharmacological interventions to prevent compulsive patterns of drug intake in at-risk populations, and to reduce or eliminate compulsive drug use in populations already diagnosed with a substance use disorder. Although research examining aerobic exercise and substance abuse is far from complete, a sufficient amount of preclinical data now exists to support the design and implementation of exercise-based interventions in substance-abusing populations.

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