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PHYSICAL ACTIVITY AND REWARD

The role of dopamine

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The idea that physical activity could be rewarding may seem counter-intuitive because many people find exercise aversive and would prefer to be inactive. Arguably one of the greatest health problems facing the United States today is inactivity, which is associated with obesity and metabolic syndrome, e.g., diabetes, heart disease, and stroke (Must et al., 1999). On the other hand, clearly, certain individual humans find at least some types of physical activity rewarding, as they choose to exercise multiple times per week and even report that they feel euphoria from exercise, as in the case of the runner's high (Boecker et al., 2008). Moreover, many people who regularly exercise report withdrawal symptoms if they are unable to exercise, including irritability, anxiety, difficult time focusing, and bad mood (Mondin et al., 1996). Hence, in certain predisposed humans, it seems that physical activity can be rewarding and reinforcing to the extent that individuals choose to engage in the activities and show withdrawal when prevented from an exercise routine.

In industrialized nations such as the United States where physical activity is typically low, individuals who find exercise rewarding and reinforcing have a health advantage because regular bouts of aerobic physical exercise maintain cardiovascular, immune, and mental health, and delay aging. Exercise reverses many of the causes and symptoms of metabolic syndrome by reducing body fat, increasing sensitivity of insulin receptors, and decreasing blood pressure (when not exercising) (Helmrich, Ragland, Leung, & Paffenbarger, 1991). Exercise also appears to enhance brain health. For example, in humans and rodent models, exercise improves performance on cognitive tasks and can reduce stress and aging-induced cognitive deficits (Colcombe & Kramer, 2003; Greenwood & Fleshner, 2011). Therefore, understanding the mechanisms underlying reward and motivation for physical activity has broad implications for improving health and longevity.

Behavioral evidence that physical activity can be rewarding in animals

Cumulative evidence from the animal literature supports the contention that physical activity can be rewarding. First, many animals will work for access to physical activity in an operant conditioning task (Iversen, 1993). In addition, studies have established that rats prefer to spend time in environments paired with the aftereffects of wheel running using the conditioned place preference (CPP) assay (Belke & Wagner, 2005; Lett, Grant, Byrne, & Koh, 2000). One

limitation is that it is not clear whether physical activity per se was rewarding or whether access to the running wheel served as a form of enrichment for the animals. In other words, animals housed in standard laboratory cages could have been relatively deprived of stimuli, and the wheel provides a novel stimulus for the animals. Seeking a more enriched experience could explain why animals chose to press levers to obtain access to a running wheel and showed preference for contexts paired with a wheel.

On the other hand, a large body of literature has established that many animals choose to run long distances when presented with the opportunity even when there is no clear goal or objective (e.g., to obtain food, water, or mates). Moreover, animals will engage in the physical activity repeatedly over weeks and months, long after the stimulus or experience could have been perceived as novel. For example, standard inbred strains of mice run between 2 and 10 km/day, depending on the genotype, when running wheels are available (Clark, Kohman et al., 2011). Hence, combined with the operant and classical conditioning data, the cumulative evidence favors the hypothesis that physical activity itself can be rewarding and reinforcing in animals.

Neurobiological indicators of physical activity reward

A number of rodent animal studies have discovered neurobiological changes induced from chronic voluntary wheel running that are analogous to changes that take place in the brain in response to drugs of abuse (Greenwood et al., 2011; Rhodes, Garland, & Gammie, 2003; Werme, Thoren, Olson, & Brene, 2000). If one assumes that the molecular changes induced from chronic drugs reflect the rewarding properties of the drugs, then these data provide additional evidence that physical activity can be rewarding and reinforcing, similar to drugs of abuse. However, despite the massive drug abuse literature, it is difficult to prove that a specific molecule is involved in rewarding as opposed to aversive properties of drugs, their side effects, or compensatory mechanisms associated with chronic drug administration not directly related to reward (Rhodes & Crabbe, 2005). Most proposed causal molecular mechanisms for addiction and reward remain contentious in the field. However, in one group of relatively convincing studies, Werme et al. (2002) found that rats that ran for 30 days at approximately 10 km/day displayed increased levels of ΔFosB in the nucleus accumbens compared to rats exposed to locked running wheels. Similar increases in ΔFosB occurred in rats exposed to chronic drugs of abuse (Perrotti et al., 2008). Moreover, mice that overexpressed ΔFosB selectively in striatal dynorphin-containing neurons increased their daily running compared with control littermates, consistent with previous work showing ΔFosB overexpression within this same neuronal population increases the rewarding properties of drugs of abuse (Werme et al., 2002). Based on the observations that ΔFosB accumulates in the nucleus accumbens and striatum with repeated drug use and is sufficient to induce drug-seeking behavior, ΔFosB has been suggested to be a molecular switch for addiction (Nestler, Barrot, & Self, 2001). It is known that ΔFosB is a transcription factor, i.e., it binds to protein complexes that bind to DNA to cause the expression of genes (Nestler, Kelz, & Chen, 1999). However, how exactly ΔFosB contributes to reward or addiction, and the specificity of ΔFosB in reward as compared to aversion is not known and remains an active area of research. For example, ΔFosB is induced from a variety of stimuli in addition to drugs of abuse and wheel running, including electroconvulsive seizures, brain lesions, and chronic stress (Chen, Kelz, Hope, Nakabeppu, & Nestler, 1997; Vialou et al., 2010). Taken together, the available data suggest that ΔFosB may be an important molecule involved in the reinforcing effects of physical activity and drugs of abuse, but how ΔFosB contributes to the perception of reward or reinforcement and the specificity of the ΔFosB response to reward has not been established.

Replicate lines of mice selectively bred for increased voluntary wheel running behavior

Additional neurobiological evidence that physical activity can be rewarding and reinforcing comes from a long-term selective breeding experiment for increased voluntary wheel running behavior in mice (Swallow, Carter, & Garland, 1998). The experiment began in 1993 and is still ongoing. Mice generated from this experiment represent an invaluable resource for discovering common mechanisms underlying physical activity reward. One of the great strengths of the model is the replication of the lines. An unprecedented four replicate high-runner lines and four replicate control lines are maintained. The replication of the lines combined with the large divergence in levels of voluntary wheel running produced over 18 years and 60+ generations of breeding provides a unique and statistically powerful genetic animal model to identify neurobiological mechanisms underlying the increase in the running behavior (Rhodes, Gammie, & Garland, 2005).

Note that there is no a priori reason why increased voluntary running induced from selection would have to involve changes in brain reward circuits. For example, changes in exercise-physiological traits such as increases in mitochondria in muscles or size of the heart could have changed to allow the animals to run farther. In fact, the original rationale for conducting the experiment was to identify correlated changes in exercise-physiological traits (such as heart mass or aerobic capacity) – not brain reward – that were hypothesized to support the high activity levels (Swallow, Garland, Carter, Zhan, & Sieck, 1998). A number of exercise-physiological changes have been documented in the lines including a small muscle phenotype with high concentration of enzymes involved in aerobic metabolism (Guderley, Joanisse, Mokas, Bilodeau, & Garland, 2008). Moreover, aerobic capacity, the maximum amount of oxygen an animal can consume during forced exercise, has increased in the high-runner lines (Rezende, Garland, Chappell, Malisch, & Gomes, 2006). Nonetheless, a number of pieces of evidence that will be reviewed in this chapter also suggest that the brain reward circuit has undergone substantial evolution to cause increased motivation for running in the high-runner lines. In retrospect, it is intuitive that selection on a voluntary behavior would have to involve changes in brain reward circuits given that at the start of the experiment most of the animals probably did not choose to run at maximum physiological capacity, and therefore individual differences in levels of running were most likely attributed to differences in perceptions of reward or motivation for the activity.

Over the years of selection, voluntary levels of running increased in the high-runner lines from an average of approximately 4 km/day at the start of the experiment, up to an average of 15 km/day by generation 15. After generation 15, levels of running reached a plateau and have remained at approximately a 15-km/day average through the current generations. A pivotal experiment was conducted in generation 29 that identified brain regions in the high-runner mice putatively involved in motivation for running (Rhodes et al., 2003). Animals were placed on wheels for 6 days. On day 7, during the daytime when the animals were resting, a tile was placed between the wheel access tunnel and the cage so that the animals would not be able to run during their normal active period. The other half of the animals remained undisturbed and freely able to run. All animals were euthanized at a time when they would normally be running at peak levels and their brains were removed and processed to measure patterns of neuronal activation in 25 different brain regions using a standard technique described below. The idea behind the blocked running group was to examine brain activity when animals were expecting and wanting to run but were unable to do so. Because running itself activates neuronal systems, we reasoned that if the animals were running at the time of euthanasia (as they were in the free-runner group), we would not be able to differentiate brain regions involved in motivation from brain regions merely reflecting the sensory stimulation of running itself. Hence, the animals prevented from

running were considered to be in a state of withdrawal from running, potentially involving many emotions, including frustration, anxiety, expectation, and craving, among others, most of which we argued would reflect wanting or desire to run (Rhodes et al., 2003).

Immediately after euthanasia, the brains of all the animals were removed, sectioned, and stained for immunohistochemical detection of c-Fos. c-Fos is another transcription factor like ΔFosB discussed in the preceding section, except unlike ΔFosB, c-Fos is transiently expressed in response to a stimulus, reaching peak concentrations approximately 2 hours after a stimulus and then rapidly degrading to undetectable levels rather than accumulating with repeated exposures as does ΔFosB (Nestler et al., 2001). The technique of immunohistochemical detection of c-Fos is widely used to capture and quantify neuronal activation occurring up to 2 hours in the brain before animals are euthanized (Clark, Bhattacharya, Miller, & Rhodes, 2011). Neurons that were stimulated or firing action potentials to a large enough degree to induce a transcriptional response within the cells during this period will express high levels of c-Fos and appear darkly stained under the microscope (Clayton, 2000) (see Figure 4.1).

We observed a striking and surprising result. Many brain regions that are classically considered components of the natural reward circuit (see below) displayed high numbers of c-Fos-positive cells in the animals prevented from running (Rhodes et al., 2003). An example is shown in Figure 4.1 for the dorsal striatum. Similar patterns of c-Fos were observed when animals were exposed to contexts paired with drugs of abuse (Johnson, Revis, Burdick, & Rhodes, 2010; Rhodes, Ryabinin, & Crabbe, 2005; Zombeck et al., 2008). Perhaps even more striking was that animals from the selected high-runner lines displayed significantly greater c-Fos responses in these reward regions as compared to control unselected animals. Although high-runner animals are more active than controls in cages without running wheels (Malisch et al., 2009; Rhodes et al., 2001), we concluded that differences in physical activity were unlikely to account for the c-Fos responses in reward regions when animals were prevented from running. This is because the complementary group of animals that were freely able to run up to the point of euthanasia displayed low c-Fos levels in these regions and the c-Fos levels were uncorrelated with individual differences in running behavior. Hence, we concluded that components of the natural reward circuit in the brain had undergone evolutionary changes in the high-runner lines to predispose high motivation for running (Rhodes et al., 2003).

The natural reward circuit and the role of dopamine in the brain

The natural reward circuit (see Figure 4.2) can be defined as the set of brain regions involved in the perception of pleasure from rewarding experiences leading to reinforcement of behaviors involved in seeking the experience. Such a circuit is hypothesized to have evolved to enable animals to behave in ways that increase survival and reproductive success. The identity of some of the key brain regions comprising the natural reward circuit was originally discovered by Olds and Milner in 1954 (Olds & Milner, 1954) using electrodes placed in the brains of rats performing an operant task to deliver mild electric shocks in the region where the electrode was placed. They discovered that a rat would repeatedly press the lever to self-administer shocks when the electrode was placed at many different regions throughout the brain. However, when the electrode was placed anywhere near the medial forebrain bundle, a group of axons connecting the septal area, lateral hypothalamus, nucleus accumbens, and ventral tegmental area (VTA) of the brain, the effect was particularly pronounced, oftentimes resulting in the animals forgoing food and water in order to continue lever-pressing. The interpretation was that electrical activation of the medial forebrain bundle results in perception of pleasure similar to but on a much larger scale compared to physiological activation produced by natural rewards such as food and sex.

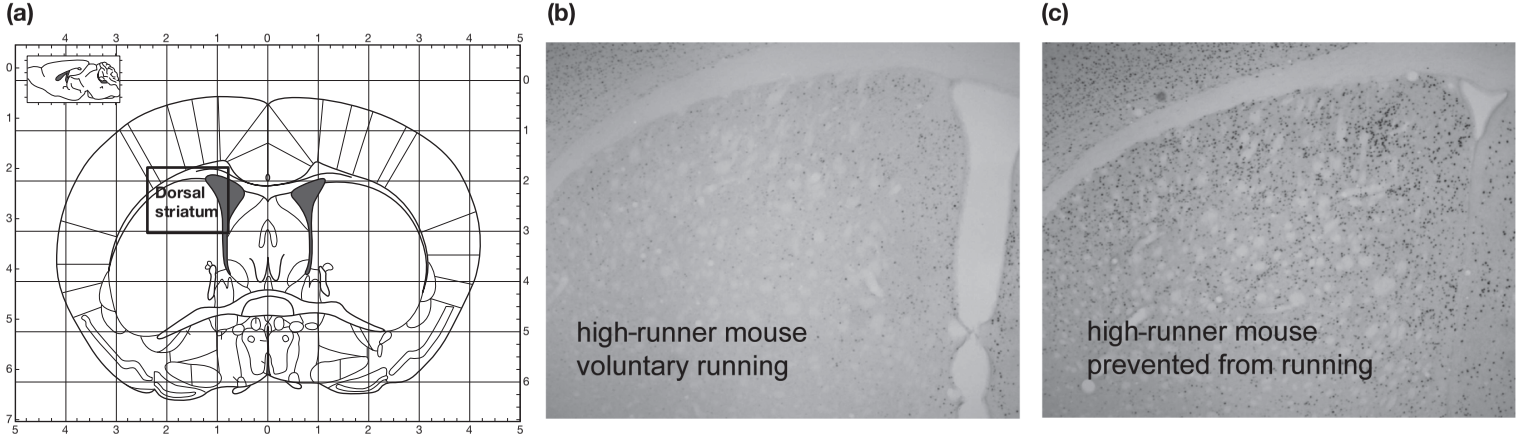


Figure 4.1 Brain activation in dopaminergic regions reflects intrinsic motivation to run. Panel A shows a diagram of a coronal section through a mouse brain, where numbers of c-Fos cells were analyzed in the dorsal striatum, a major site of innervation from ventral midbrain dopamine neuron projections. The box indicates the approximate location of the photographs in B and C. The dots in the photographs are neuronal nuclei expressing relatively high levels of c-Fos protein, indicating transcriptional activation from running or wanting to run. The photograph in panel B is a representative sample from a high-runner mouse that is freely running at the time of euthanasia. The photograph in panel C is a representative sample from a high-runner mouse prevented from running (a tile was placed between the wheel access tunnel and the cage). The numbers of c-Fos nuclei are counted to provide a quantitative measure of neuronal activation.

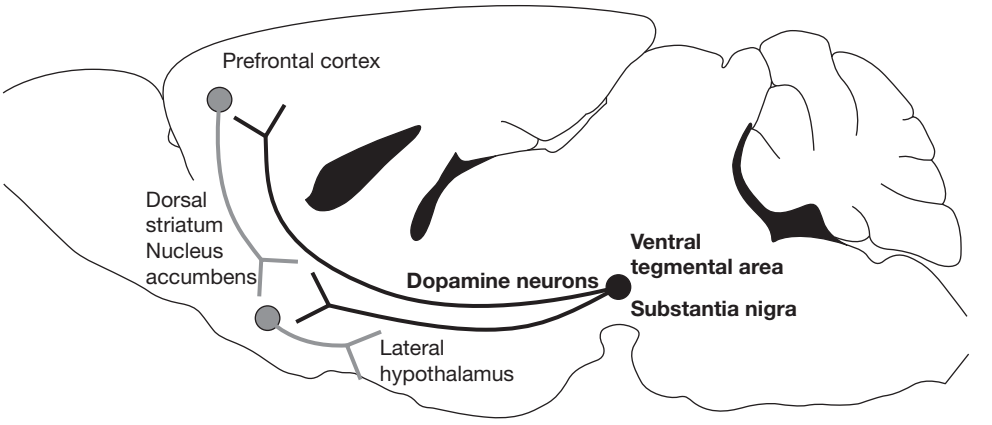


Figure 4.2 The natural reward circuit. A sagittal section of a mouse brain illustrating the location of the ventral midbrain dopamine neuron cell bodies and major projections to the dorsal striatum, nucleus accumbens, and prefrontal cortex. Interconnections with the lateral hypothalamus are shown for reference with the text. Many other brain regions contribute to the natural reward circuit. The full collection is arguably most of the brain. This is not surprising given the importance of the circuit for motivating animals to behave in ways that increase survival and reproductive success.

The VTA is one of the two main locations in the brain where neurons are located that synthesize and release dopamine, and the projection of dopamine neurons from the VTA to the nucleus accumbens is considered a key component, or final common pathway, involved in the perception of reward and reinforcement. All drugs of abuse with diverse mechanisms of action, including ethanol, cocaine, heroin, nicotine, and marijuana, and natural rewards such as food and sex increase dopamine in extracellular spaces in the nucleus accumbens (Damsma, Pfaus, Wenkstern, Phillips, & Fibiger, 1992; Doyon et al., 2003; Hernandez & Hoebel, 1988; Nisell, Nomikos, & Svensson, 1994; Tanda, Pontieri, & Di Chiara, 1997). For a long time, these findings, among many others, led to the belief that dopamine was the neurochemical substrate for reward. However, it is now established and well appreciated that dopamine plays a much more complicated role in the brain than simply acting as the reward substrate (Salamone, Correa, Mingote, & Weber, 2005). Many other stimuli that produce strong aversion or the opposite of pleasure, such as pain or stress, also induce dopamine release into the nucleus accumbens (Scott, Heitzeg, Koeppe, Stohler, & Zubieta, 2006). Moreover, dopamine has diverse functions in the brain depending on the environmental context and neuroanatomical region.

As mentioned above, dopamine projections from the VTA to the nucleus accumbens are thought to play an important role in reward and reinforcement. The VTA also makes more diffuse projections to the prefrontal and cingulate cortices and these connections, together with the accumbens, are referred to as the mesolimbic dopamine reward pathway. It is rather unfortunate that the pathway is referred to as the reward pathway because it could just as well be referred to as the aversion pathway. Rather than playing a specific role in reward, the current understanding is that dopamine in the mesolimbic circuit acts as a salience detector (Horvitz, 2000). In other words, dopamine is important for the animal to evaluate the relative importance of the stimulus for survival or reproductive success. A sudden approach of a predator that threatens the animal's life is a salient event, even more salient than finding a large meal after going hungry for several days, and both will involve dopamine release and reinforcement learning.

By acting as a salience detector, dopamine plays a pivotal role in reinforcement. This is most easily illustrated with an example. In a series of pioneering studies, Wolfram Schultz recorded the discharge of dopamine cells located in the VTA while a monkey was performing a task to obtain a juice reward (as reviewed in Schultz, 2007). What Shultz discovered is that initially, before the monkey learned the task, dopamine discharges occurred during the receipt of the unpredicted rewards. But as the monkey learned the task, the dopamine discharges began to occur in response to the cues that predicted the reward rather than from the reward itself. Moreover, if the reward was not received as expected, then depressions in discharges were observed (Fiorillo, Tobler, & Schultz, 2003). These observations are consistent with a role for dopamine in learning appropriate behaviors and associations in response to salient stimuli, in this case a juice reward.

The other main location in the brain, besides the VTA, where dopamine cell bodies reside is the substantia nigra pars compacta. The projection of dopamine neurons to the dorsal striatum, known as the nigrostriatal pathway, is part of the basal ganglia circuit that mediates the coordination of locomotor function. Loss of dopamine neurons in the nigrostriatal pathway causes Parkinson's disease and erratic, uncoordinated motor behavior. The nigrostriatal pathway is also thought to play a key role in the natural reward circuit, specifically integrating information about rewarding or aversive experiences, making decisions, and coordinating goal-directed movement toward or away from salient experiences (Wise, 2009).

A very important unresolved question is how the reward circuit is modified by experiences to produce strong reinforcement learning and compulsive behavior, as in the case of addiction or dependence. Another important unresolved question is how the reward circuit develops or functions differently to predispose individuals to engage in specific behaviors caused by genetic and/or environmental factors. The same brain regions and neurochemicals implicated in addiction are thought to be components of the natural reward circuit, and the specific differences in the circuit (e.g., more or fewer dopamine receptors of one or several types, neuroanatomical distribution, differences in numerous second messengers involved in dopamine signaling cascade, etc.) that make an animal motivated for one behavior (e.g., physical activity) versus another (e.g., drug abuse) are not known. Discovering the specificity in the neural circuits involved in drug abuse and addiction versus motivation for natural rewards is an important area for future research because it will help define the neurobiology of compulsive maladaptive behavior as compared to healthy behavior, and potentially identify useful targets for pharmacotherapy.

Dopamine signaling in physical activity reward

Given that physical activity can be inherently rewarding in animals and humans, and given the extensive literature on the role of the dopamine neurotransmitter system in reward, reinforcement, and the voluntary control of movement, it is not surprising that dopamine signaling appears to play a role in physical activity reward. Microdialysis studies, where extracellular fluid from the nucleus accumbens and dorsal striatum was sampled and analyzed for dopamine and dopamine metabolite concentrations during forced treadmill running at a variety of speeds, have been conducted in rats (for a review see Table II in Meeusen, Piacentini, & De Meirleir, 2001). The extracellular fluid was analyzed using high-performance liquid chromatography to quantify concentrations of dopamine and metabolites. It appears that a threshold speed is needed somewhere between 3 and 7 m/min for rats, but at or above this speed, dopamine concentrations in extracellular spaces increase above resting levels. Moreover, dopamine turnover, as measured by accumulation of dopamine metabolites (DOPAC and HVA) in extracellular spaces, increases linearly with the speed of running (Hattori, Naoi, & Nishino, 1994). As discussed in the previous

sections, increased extracellular dopamine does not necessarily imply reward. Dopamine signaling in the nucleus accumbens or dorsal striatum could reflect voluntary control of movement. Moreover, the dopamine signaling could simply reflect the salient experience of forced running that would occur regardless of whether the experience was perceived as aversive or rewarding.

Although the rodent animal literature consistently reports increased extracellular dopamine from treadmill running, the human literature is less consistent. A recent study conducted in humans using positron emission tomography (PET) to non-invasively quantify extracellular dopamine in the striatum found no evidence that synaptic dopamine concentrations changed in response to 30 minutes of treadmill running at a moderate intensity (approximately 10 km/hr) (Wang et al., 2000). However, the PET technique to quantify dopamine and other molecules in the rat studies is very different from microdialysis. Rather than directly measuring dopamine and metabolites from extracellular fluid in the brain, the PET method uses non-invasive imaging of radio-labeled raclopride, a dopamine D2-receptor antagonist, which is injected intravenously into the subject to estimate the magnitude of binding to D2 receptors. The theory is that raclopride will compete with endogenous dopamine for D2 receptors, and hence, if extracellular dopamine increases after exercise, it can be detected by measuring proportional decreases in binding of raclopride. A major limitation of the PET method is that receptor binding could also be influenced by changes in dopamine receptors on cellular membranes, which can be transported to and from the cytoplasm in response to local concentrations of extracellular dopamine (Dumartin et al., 2000). However, the evidence suggests that the method works for detecting large changes in extracellular dopamine such as that induced from stimulant drugs that block dopamine uptake. Simultaneous microdialysis and PET imaging studies in nonhuman primates have shown a linear relation between the changes in dopamine induced from stimulant drugs as assessed with microdialysis and those obtained using imaging (Breier et al., 1997; Laruelle et al., 1997). Therefore, the method appears to work for detecting large dopamine fluctuations, but it may be limited for detecting smaller changes such as those induced from running on a treadmill.

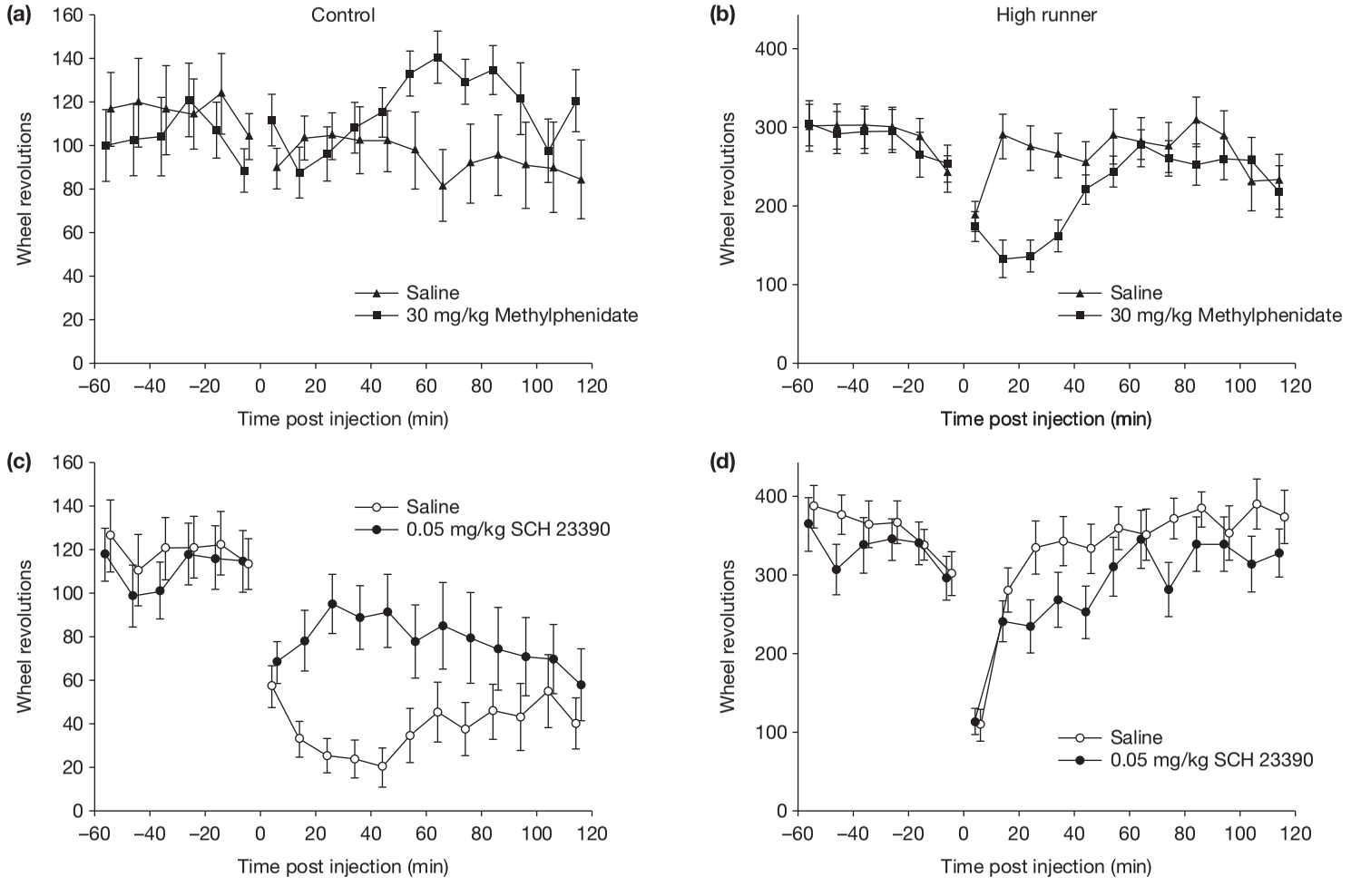
Additional evidence that the dopamine neurotransmitter system is involved with motivation for physical activity comes from a study using mice deficient in expression of the Nurr1 gene, a gene involved in the development of midbrain dopamine neurons (Werme et al., 2003). Mice were engineered to carry a null mutation that prevents transcription of Nurr1. Heterozygous mice, deficient in Nurr1 because they carry one copy of the mutation and one copy of an intact Nurr1 gene, were compared to "wild-type" littermates carrying two intact Nurr1 copies in levels of voluntary wheel running displayed over 21 days. The heterozygous Nurr1 deficient mice displayed reduced dopamine levels in the striatum and low levels of wheel running (approximately 2 km/day) compared to their wild-type littermates (approximately 10 km/day). Hence, the authors concluded that dopamine plays a role in motivation for voluntary wheel running behavior because the dopamine deficient mice displayed low levels of running. However, another interpretation is that the dopamine deficiency impaired voluntary control of movement rather than affecting physical activity reward. Given that dopamine is required to control voluntary movement, it is possible that the dopamine deficient mice ran less not because they found physical activity less rewarding than wild-type mice but rather because they were unable to control their movement sufficiently to produce high levels of running. The authors favored the reward hypothesis because the dopamine deficient mice also drank less ethanol than wild-type mice, suggesting that they were less motivated for both natural and drug rewards. They ruled out the possibility that a mild motor impairment could affect ethanol drinking by showing that the dopamine deficiency did not affect intake of a sweetened or bitter solution (see Figure 2A, B in Werme et al., 2003). However, it is possible that drinking is not as difficult a motor task as running on a wheel, and that the mild motor impairment could still have caused the reduced wheel running.

The specificity of dopamine involvement in physical activity reward as compared to a more general role in processing salient experiences or voluntary control of movement is difficult to establish. However, the lines of mice selectively bred for increased voluntary wheel running described above provide additional evidence that seems to tip the balance in favor of the reward hypothesis. In a series of studies, it was demonstrated that the high runners respond very differently to drugs that increase dopamine in extracellular spaces (including methylphenidate, cocaine, and GBR12909). In high-runner lines, these drugs tend to reduce running, whereas at similar doses in control unselected mice, these drugs either had no effect or increased running (Rhodes & Garland, 2003; Rhodes et al., 2001). The difference is particularly striking because the increased distances run in high-runner lines are primarily due to increased speeds of running rather than increased duration of running, and the drugs mainly reduced running speed, not duration. Both control and high-runner mice spend most of the dark cycle running; the high runners just run faster during these running bouts (Girard, McAleer, Rhodes, & Garland, 2001). Hence, by artificially increasing dopamine in extracellular spaces using drugs, it is possible to turn a high runner into an animal that appears more like a mouse from a control unselected line. Methylphenidate data are shown in Figure 4.3A and B to illustrate the general result.

Additional experiments examining the effects of dopamine agonists and antagonists on wheel running behavior in the replicate high-runner and control lines suggest that dopamine signaling via D1-like receptors has likely been altered by selection. Specifically, high-runner mice were significantly less sensitive to the locomotor-reducing effects of dopamine D1-like but not D2-like antagonists. Figure 4.3C and D illustrate the result for the dopamine D1-like antagonist drug SCH23390. At a dose of 0.05 mg/kg, SCH23390 severely reduces wheel running in control unselected mice, whereas it barely has any effect in mice from high-runner lines. No differences were observed between high-runner and control mice in response to the serotonin reuptake inhibitor fluoxetine and the mu-opioid receptor antagonists naloxone and naltrexone. All these drugs dose dependently decreased wheel running to a similar extent in all the lines (Li, Rhodes, Girard, Gammie, & Garland, 2004; Rhodes et al., 2001). Hence, the behavioral pharmacology data specifically identify the dopamine neurotransmitter system as being changed in some way from selection and not the other candidates examined including opioid and serotonin systems.

Our current hypothesis is that specific molecules downstream of dopamine D1-receptors are altered in high-runner mice and that these molecular differences contribute to the altered sensitivity to dopamine drugs and increased motivation for physical activity. We first considered the possibility that dopamine levels or dopamine turnover or metabolism could explain the pharmacology results. However, high runners and controls showed no detectable differences in total dopamine concentrations or dopamine metabolites in the striatum under resting conditions or when forced to run on a treadmill at varying speeds (Rhodes, Gammie, & Garland, 2005). We also considered the possibility that dopamine D1 or D2 receptors were differentially expressed in the striatum. However, no significant differences were detectable using standard radio-ligand binding assays (unpublished data). Therefore, our current hypothesis is that intracellular molecules

Figure 4.3 Dopamine D1-like receptor signaling implicated in high voluntary wheel running behavior. Mean wheel running (revolutions) ± SEM is plotted in 10-min increments 1 h before and 2 h after an injection of either saline or methylphenidate (Ritalin) (30 mg/kg) (n = 24 per data point). Panel A shows data for unselected control lines and panel B for high-runner lines. Methylphenidate increased wheel running in control lines and decreased running in high-runner lines. Panels B and C show the same graphs as A and B except in response to a dopamine D1-like receptor antagonist, SCH 23390. High-runner mice were less sensitive than controls to the behavioral effects of SCH 23390. Panels A–D are redrawn from Rhodes & Garland (2003).


(a)
Control
Wheel revolutions
Time post injection (min)
Saline
30 mg/kg Methylphenidate
(b)
High runner
Wheel revolutions
Time post injection (min)
Saline
30 mg/kg Methylphenidate
(c)
Wheel revolutions
Time post injection (min)
Saline
0.05 mg/kg SCH 23390
(d)
Wheel revolutions
Time post injection (min)
Saline
0.05 mg/kg SCH 23390

in the dopamine signaling cascade, besides dopamine and its receptors, were the direct targets of selection. The identity of these molecules is currently unknown and is the topic of future investigation. The dopamine signaling system is extraordinarily complex, with numerous molecules including those in the DARPP-32/protein phosphatase-1 cascade (Greengard, Allen, & Nairn, 1999). Many of these molecules are also influenced by receptor signaling from other neurotransmitter systems besides dopamine, such as glutamate, GABA, serotonin, and neuropeptides, thus making them attractive candidates for integrative regulation of brain function.

Future directions

The cumulative evidence that dopamine plays a role in the motivation for physical activity is convincing, but which molecules in the dopamine signaling cascade are critical regulators of physical activity reward remains presently unknown. One of the biggest challenges is identifying specificity of dopamine involvement in behavior. Dopamine is a neuromodulator in the brain with diverse functions. It regulates neuronal activation and signaling between many different types of neurons throughout the brain. Given the complexity of the system, i.e., numerous molecules with different expression patterns in different brain regions, it is not surprising that dopamine signaling serves diverse functions. Discovering which components change to increase voluntary wheel running seems a tractable goal, but will be challenging. A large literature on brain reward circuits implicated in drug abuse has yet to agree on clear molecular mechanisms leading to craving for drugs and addiction. Moreover, the specificity in the neural circuits or molecular components involved in motivation for drugs versus natural rewards and aversive stimuli is not established and will be difficult to determine (Johnson et al., 2010; Zombeck et al., 2008).

One advantage for the physical activity phenotype as compared to the drug models is the availability of the statistically powerful replicated selective breeding experiment for increased voluntary wheel running behavior. It seems plausible to use genomic approaches to identify common patterns of gene expression in brain reward regions under different conditions of voluntary wheel access in the replicate selected and unselected lines. Discovering the molecules and structural changes that are different in animals highly motivated for physical activity could provide new insight into mechanisms of behavior and motivation. Knowledge of how a brain functions to motivate physical activity has broad therapeutic applications in a modern culture where inactivity threatens health and longevity.

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